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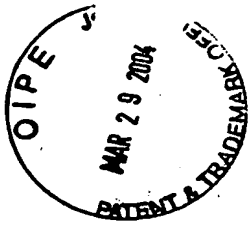
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AAAAATAAATCAT ATG AAA AAT ATT AAA AAA AAT CAA GTA ATC AAT CTC GGT CCT AAT TCT
M K N I K K N Q V M N L G P N S
AAA TTA TTA AAA GAA TAT AAA TCA CAA TTA ATT GAA TTA AAT ATT GAA CAA TTT GAA GCA
K L L K E Y K S Q L I E L N I E Q F E A
GGT ATT GGT TTA ATT TTA GGA GAT GCT TAT ATT CGT AGT CGT GAT GAA GGT AAA ACT TAT
G I G L I L G D A Y I R S R D E G K T Y
TGT ATG CAA TTT CAC TCC AAA AAT AAG GCA TAC ATG GAT CAT GTA TGT TTA TTA TAT GAT
C M Q F E W K N K A Y M D H V C L L Y D
CAA TGG GTA TTA TCA CCT CCT CAT AAA AAA GAA AGA GTT AAT CAT TTA GGT AAT TTA GTA
Q W V L S P P H K K E R V N H L G N L V
ATT ACC TGG GGA GCT CAA ACT TTT AAA CAT CAA GCT TTT AAT AAA TTA GCT AAC TTA TTT
I T W G A Q T F K H Q A F N K L A N L F
ATT GTA AAT AAT AAA CTT ATT CCT AAT AAT TTA GTT GAA AAT TAT TTA ACA CCT ATG
I Y N N K K L I P N N L V E N Y L T P M
AGT CTG GCA TAT TGG TTT ATG GAT GAT GGA GGT AAA TGG GAT TAT AAT AAA AAT TCT CTT
S L A Y W F M D D G G K W D Y N K N S L
AAT AAA AGT ATT GTA TTA AAT ACA CAA AGT TTT ACT TTT GAA GAA GTA GAA TAT TTA CTT
N K S I V L N T Q S F T F E E V C Y L V
AAA GGT TTA AGA AAT AAA TTT CAA TTA AAT TGT TAT GGT AAA ATT AAT AAA AAT AAA CCA
K G L R N K F Q L N C Y V K I N K N K P
ATT ATT TAT ATT GAT TCT AGT AGT TAT CTG ATT TTT TAT AAT TTA ATT AAA CCT TAT TTA
I I Y I I D S M S Y L I F Y N I T K P Y L
ATT CCT CAA ATG ATG TAT AAA CTG CCT AAT ACT ATT TCA TCC GAA ACT TTT TTA AAA TAA
I P Q M M Y K L P N T I S S E T F L K

FIG. 1

1 and 2: THESE AMINO ACIDS ARE ABSOLUTELY NECESSARY TO PRODUCE CATALYTIC ACTIVITY. OTHER SUBSTITUTIONS ARE POSSIBLE, SUCH AS DELETIONS OF THE 10 FIRST AMINO ACIDS.

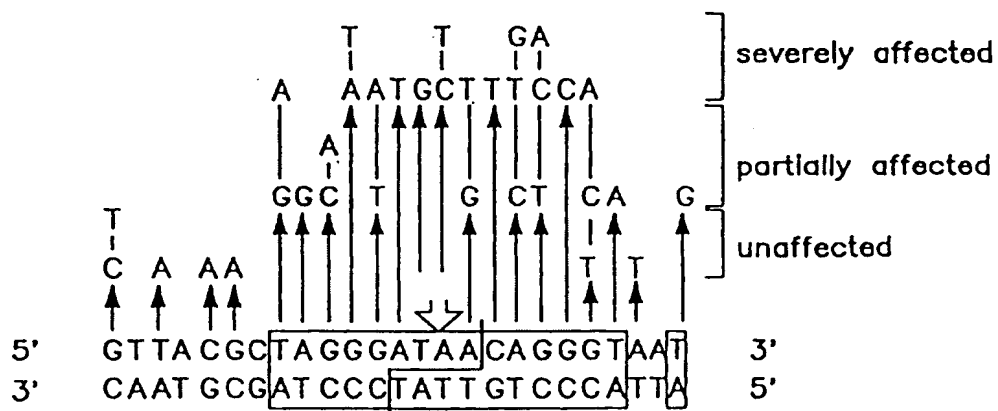
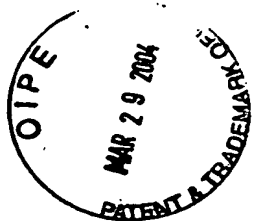
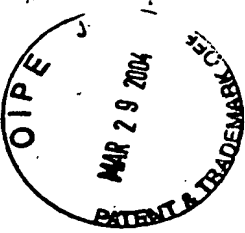
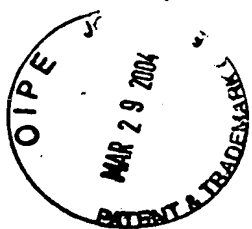


FIG. 3



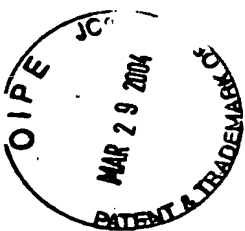
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1747 TTATAGTCCTGTGCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTGTG ATG CTC GTC AGG GGG GCG GAG 1818
1819 CCT ATG GAA AAA CGC CAG CAA CGC GGC CTT TTT ACG GTT CCT GGC CTT TTG CTG GCC TTT 1878
1879 TGC TCA CAT GTT TCC TCC TGC GTT ATC CCC TGA TTCGTGGATAACCGTATTACCGCCTTTGAGTGAGC 1947
1948 TGATACCGCTGCGCGCAGCGAACGACCGAGCGCAGTGAGCGGAGGAGCGGCAATACGCAAC 2027
2028 CGCCTCTCCCCGCGGTTGGCCGATTTCATTA ATG CAG CTG GCA CGA CAG GTT TCC CGA CTG GAA AGC 2094
2095 GGG CAG TGA GCGCAACGCAATTA ATG TGA GTTAGCTCACTCATTAGGCACCCCGGCTTTACACTTT ATG 2164
2165 CTT CCG GCT CGT ATG TTG TGT GGA ATT GTG AGC GGA TAA CAATTTACACACAGGAAACAGCT ATG 2228
2229 ACC ATG ATT ACG AAT TCT CAT GTT TGA CAGCTTATCATCGATAAGCTTTA ATG CCG TAG TTTATCAC 2295
2296 AGTTAAATTGCTAACGCAGTCAGGCACCGTGT ATG AAA TCT AAC AAT GCG CTC ATC GTC ATC CTC GGC 2363
2364 ACC GTC ACC CTG GAT GCT GTA GGC ATA GGC TTG GTT ATG CCG GTA CTG CCG GGC CTC TTG 2423
2424 CGG GAT ATC CGC CTG ATG GAA CGT GAC GGA CGT AAC CAC CGC GAC ATG TGT GTG CTG 2483
2484 TTC CGC TGG GCA TGC CAG GAC AAC TTC TGG TCC GGT AAC GTG CTG AGC CCG GCC AAG CTT 2543

FIG. 4A



2544 73	ACT T	CCC P	CAT H	CCC P	GTT V	GAC D	AAT N	TAA	TCATCGGCTCGTATA	ATG M	TGT C	GGA G	ATT I	GTG V	AGC S	GGA G	2606 7			
2607 8	TAA	CAATTTCACACAGGAACAGGATCC	BamHI ATG CAT ATG AAA AAC ATC AAA AAA AAC CAG GTA ATG M H M K N I K K N Q V M														2670 12			
2671 13	AAC N	CTG L	GGT G	CCG P	AAC N	TCT S	AAA K	CTG L	AAA E	TAC Y	AAA K	TCC S	CAG Q	CTG L	ATC I	GAA E	CTG L	AAC N	2730 32	
2731 33	ATC I	GAA E	CAG Q	TTC F	GAA E	GCA A	GGT G	ATC I	CTG L	ATC I	CTG L	GGT G	GAT A	TAC Y	ATC I	CGT R	TCT S	CGT R	2790 52	
2791 53	GAT D	GAA E	GGT G	AAA K	ACC T	TAC Y	TGT C	ATG Q	CAG Q	TTC F	GAG E	AAA K	AAC N	GCA A	TAC Y	ATG M	GAC D	CAC H	2850 72	
2851 73	GTA V	TGT C	CTG L	TAC L	GAT Y	GAT D	CAG Q	TGG W	GTA V	CTG L	TCC S	CCG P	CAC H	AAA K	GAA E	CGT R	GTT V	AAC N	2910 92	
2911 93	CAC H	CTG L	GGT G	AAC N	CTG L	GTA V	ATC I	TGG W	GGC G	ACC A	CTG L	CTG L	TTC F	AAA K	CAC H	GCT A	TTC F	AAC N	2970 112	
2971 113	AAA K	CTG L	GCT A	AAC N	CTG L	TTC F	ATC I	AAC N	AAA K	AAA K	ACC T	ATC I	CCG P	AAC N	AAC N	CTG L	GTT V	GAA E	3030 132	
3031 133	AAC N	TAC Y	CTG L	ACC T	CCG P	ATG M	TCT S	CTG L	GCA A	TAC Y	TGG W	TTC F	ATG D	GAT G	GGT G	AAA K	TGG W	GAT D	3090 152	
3091 153	TAC Y	AAC N	AAA K	TCT S	ACC T	AAC N	CTG L	ATC I	CTG L	ATC I	GTA V	CTG L	ACC T	CAG Q	TCT S	ATC I	TTC F	GAA E	3150 172	
3151 173	GAA E	GTA V	GAA E	TAC Y	CTG L	GTT V	AAG K	GGT G	CTG L	CTG L	CTG L	CTG L	CTG L	CTG L	TGT C	TAC Y	GTA V	AAA K	3210 192	
3211 193	ATC I	AAC N	AAA K	AAC N	AAA K	CCG P	ATC I	TAC Y	ATC I	TCT S	ATG M	TCT S	TAC Y	CTG L	ATC I	TTC F	TAC Y	AAC N	3270 212	
3271 213	CTG L	ATC I	AAA K	CCG P	TAC Y	CTG L	ATC I	CCG P	CAG Q	ATG M	TAC Y	AAA K	CTG L	CCG P	AAC N	ACT I	TCC S	TCC S	3330 232	
3331 233	GAA E	ACT T	TTC F	CTG L	AAA K	TAA	Salt PstI TAAGTCGACCTGCAGCCCAAGCTTGGCACTGGCCGTCGTTTACACGTCGTGACT M Y K L P N I I S S													3404 238

FIG. 4B



		-2	-1	1				5				10							
		M	H	M	K	N	I	K	K	N	Q	V	M	N	L	G	P	N	S
			20										30						
K	L	L	K	E	Y	K	S	Q	L	I	E	L	N	I	E	Q	F	E	A
			40										50						
G	I	G	L	I	L	G	D	A	Y	I	R	S	R	D	E	G	K	T	Y
			60										70						
C	M	Q	F	E	W	K	N	K	A	Y	M	D	H	V	C	L	L	Y	C
			80										90						
Q	W	Y	L	S	P	P	H	K	K	E	R	Y	N	H	L	G	N	L	Y
			100										110						
I	T	W	G	A	Q	T	F	K	H	Q	A	F	N	K	L	A	N	L	F
			120										130						
I	V	N	N	K	K	I	I	P	N	N	L	V	E	N	Y	L	T	P	M
			140										150						
G	L	A	Y	W	P	M	D	D	G	G	K	W	D	Y	N	K	N	S	I
			160										170						
N	K	S	I	V	L	N	T	Q	S	F	T	F	E	E	V	E	Y	L	V
			180										190						
K	G	L	R	N	K	F	Q	L	N	C	Y	V	K	I	N	K	N	K	P
			200										210						
I	I	Y	I	D	S	M	S	Y	L	I	F	Y	N	L	I	K	P	Y	L
			220										230						
I	P	Q	M	M	Y	K	L	P	N	T	I	S	S	E	T	F	L	K	*

Positions that can be changed without affecting enzyme activity (demonstrated)
positions -1 and -2 are not natural. The two amino acids are added due to cloning strategies

positions 1 to 10: can be deleted
position 36: G is tolerated
position 40: M or V are tolerated
position 41: S or N are tolerated
position 43: A is tolerated
position 46: V or N are tolerated
position 91: A is tolerated
positions 123 and 156: L are tolerated
position 223: A and S are tolerated

Changes that affect enzyme activity (demonstrated)

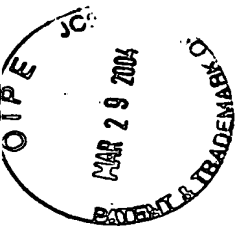
position 19: L to S
position 38: I to S or N
position 39: G to D or R
position 40: L to Q
position 42: L to R
position 44: D to E, G or H
position 45: A to E or D
position 46: Y to D
position 47: I to R or N
position 80: L to S
position 144: D to E
position 145: D to E
position 146: G to E
position 147: G to E

FIG. 5

Group I Intron Encoded Endonucleases and Related Endonucleases

ENDONUCLEASE		RECOGNITION SEQUENCE	CLEAVAGE SITE	▽ INTRON SITE
TWO DODECAPEPTIDE FAMILY (OR 4 BP CUTTERS)	I-Sce I (<i>Saccharomyces</i> mitochondria)	CGC TAGGGATAA CAGGGTAAT ATAGC GCG ATCCCTATTGT CCCATTAT ATCG		
	I-Sce IV (<i>Saccharomyces</i> mitochondria)	TTCTCATGATTAGCTCTAATCCATGG AAGAGTACTAATCGAGATTAGGTACC		
	I-Sce II (<i>Saccharomyces</i> mitochondria)	CTTTGGTCAATCAGAAAGTATATATTT GAAACCACTAGGTCTTCATATATAAA		
	I-Ceu I (<i>Chlamydomonas</i> chloroplast)	TAA CGGTCCIAAGGTAGCGAAATTCA ATTGCCAGGATTCCATCGCTTTAAGT		
	I-Ppo I (<i>Physarum</i> nucleus)	TGACTCTCTTAAAGGTAGCCAAATGCC ACTGAGAGAATTCCATCGGTTTACGG		
	I-Sce III (<i>Saccharomyces</i> mitochondria)	GGAGGTTTTGGTAACTATTTATTACC CCTCCAAAACCATTGATAAATAATGG		
	I-Cre I (<i>Chlamydomonas</i> chloroplast)	GGGTTCAAACGTCGTGAGACAGTTT CCCAAGTTTTGCAGCACTCTGTCAA		
	Endo. Sce I(RF3) (<i>Saccharomyces</i> mitochondria) (Non intronic)	GATGCTGTAGGCATAGGCTTGTTAT CTACGACATCCGTATCCGAACCAATA		
	HO (<i>Saccharomyces</i> nucleus) (Non intronic)	CTTTCCGCAACAGTATAATTTTATAA GAAAGGCGTTGTCAATTAAAAATATT		
	I-Csm I (<i>Chlamydomonas</i> mitochondria) (Putative endonuclease)	ACCATGGGGTCAAATGTCTTTCTGGG TGGTACCCAGTTTACAGAAAGACCC		
OTHER STRUCTURAL FAMILIES	(Bacteriophage T4)			
	I Tev I	CAACGCTCAGTAGATGTTTTCTTGGGTCTACCGTTTAAAT GTTGCGAGTCATCTACAAAGAACCCAGATGGCAAATTA		
	I Tev II	CAAGCTTATGAGTATGAAGTGAACACGTTATT GTTCGAATACTCATACTTCACTTGTGCAATAA		
	I Tev III	GCTATTTCGTTTTATGATCTTTTGGCTGTAGCTTTAA CGATAAGCAAAAATACATAGAAAACGCACATCGAAATT		

FIG. 6



EXPRESSION VECTORS

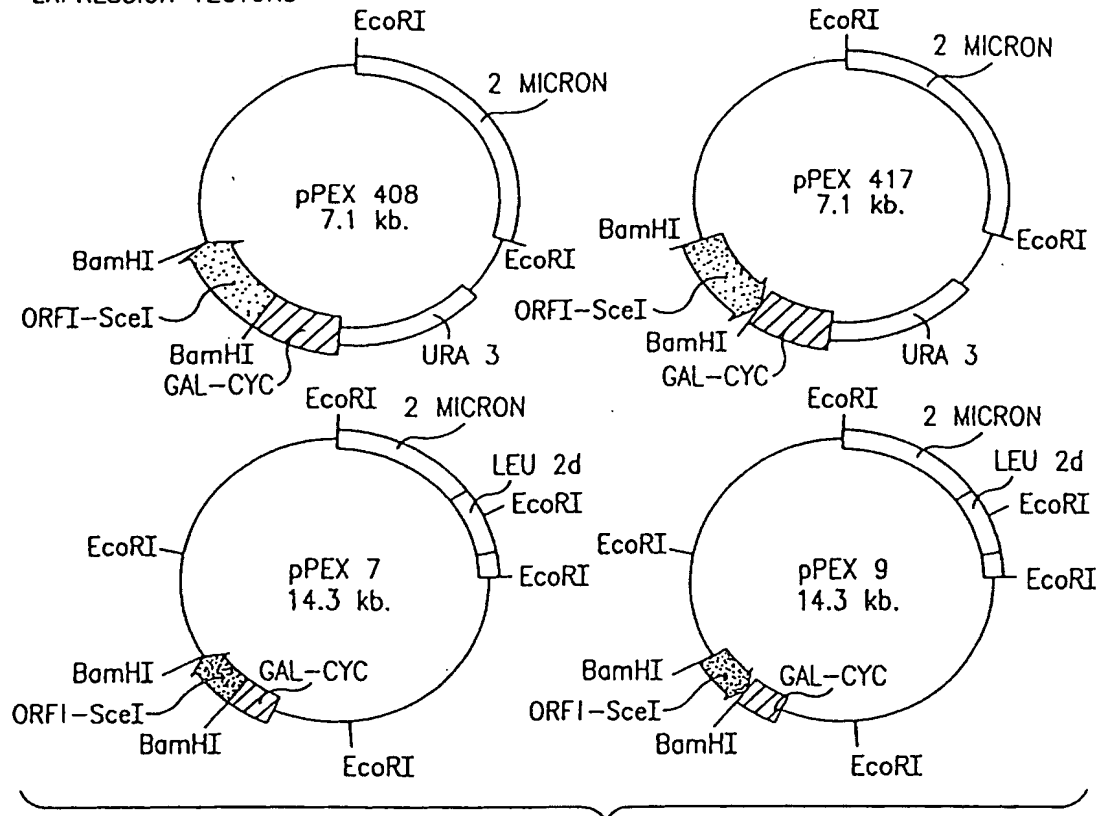


FIG. 7

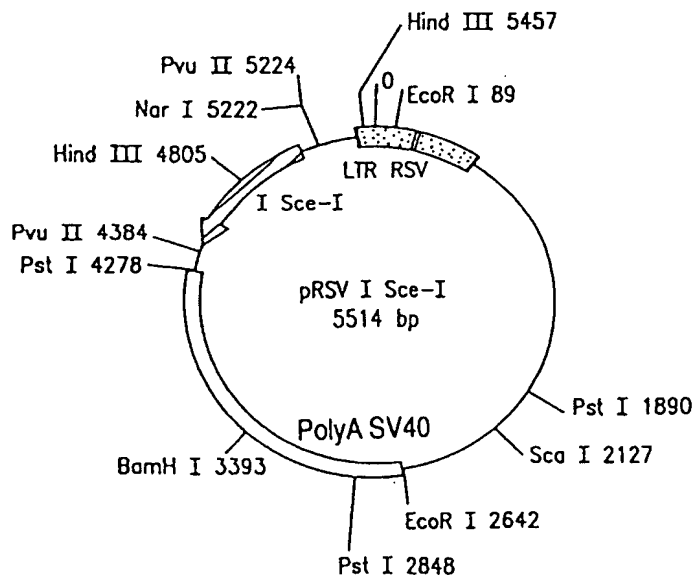


FIG. 8

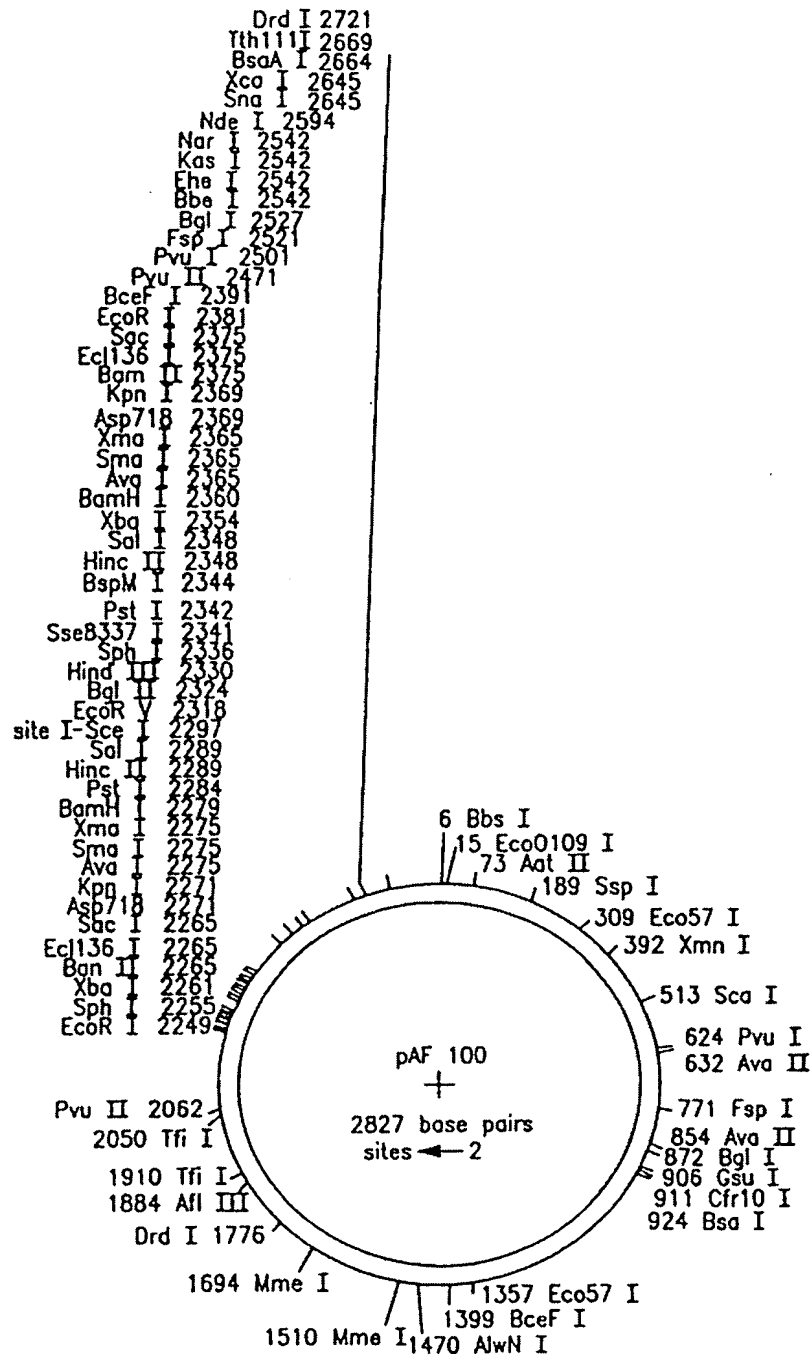
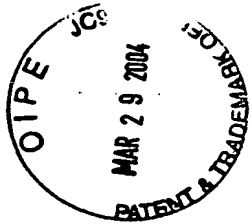


FIG. 9

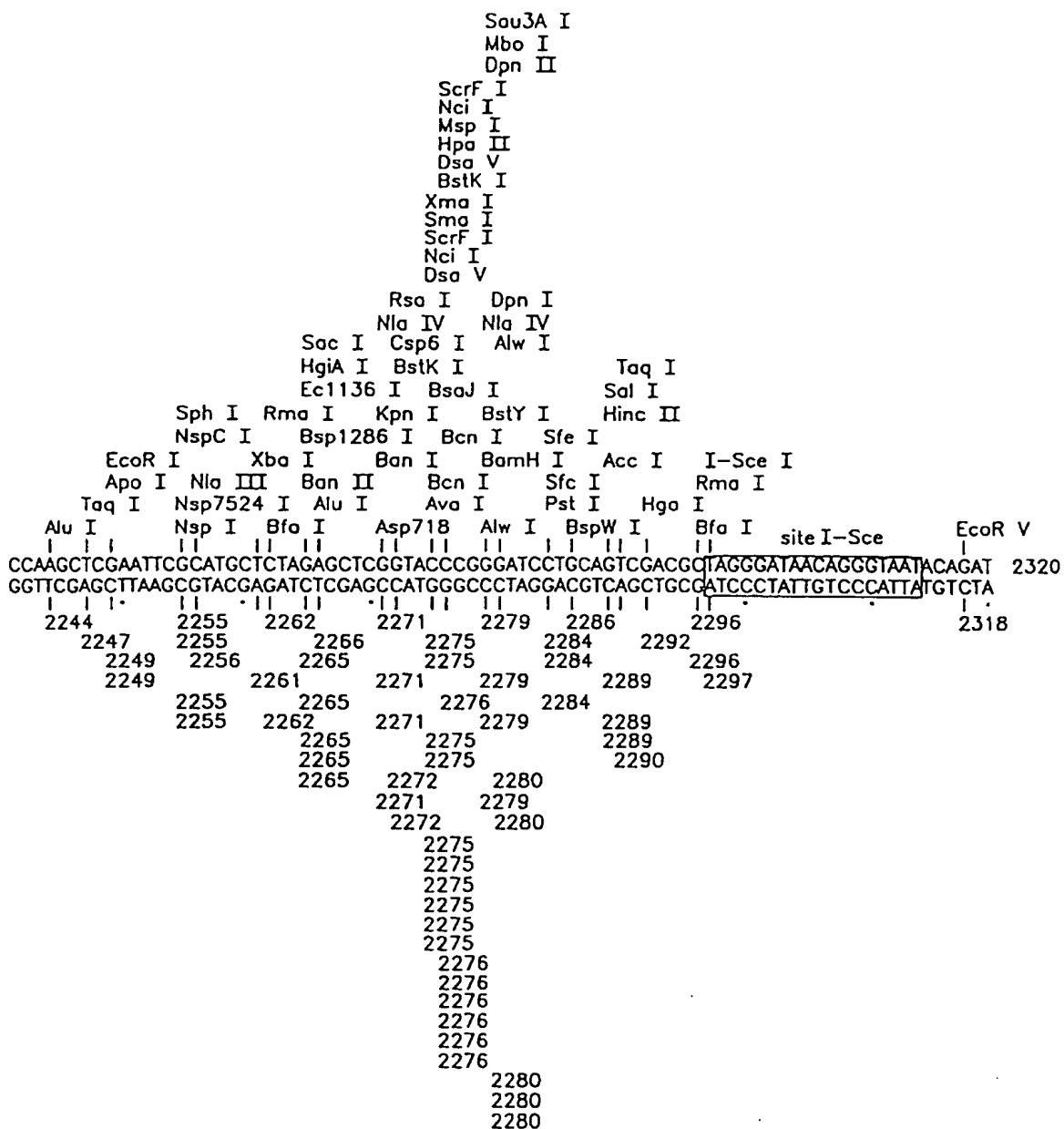
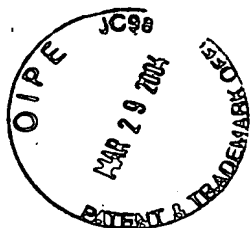


FIG. IOA

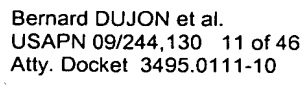
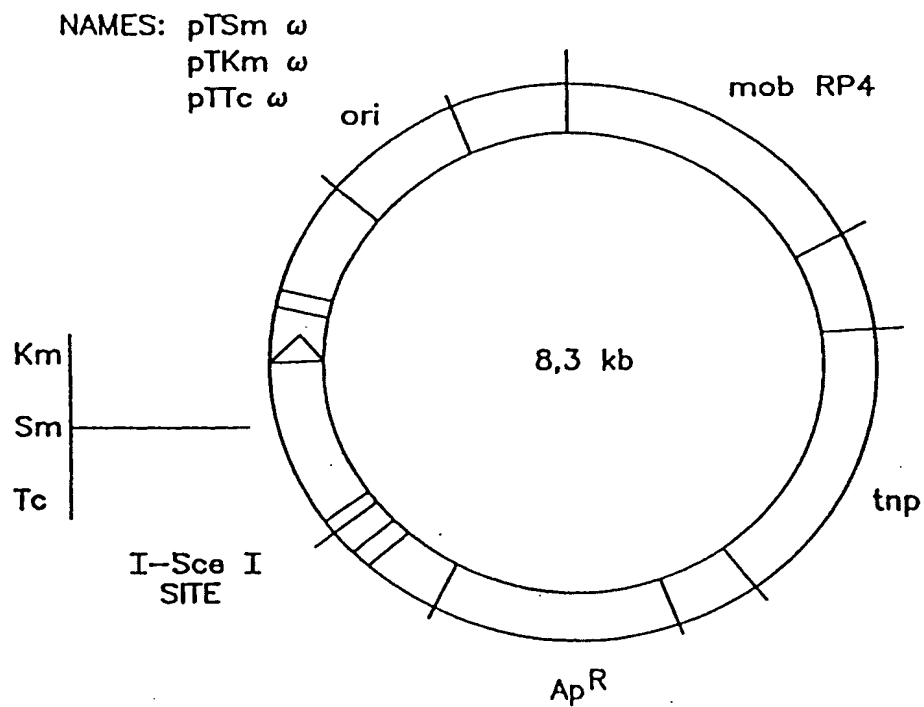
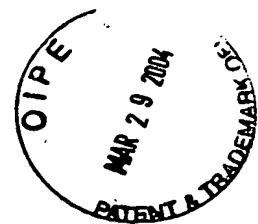
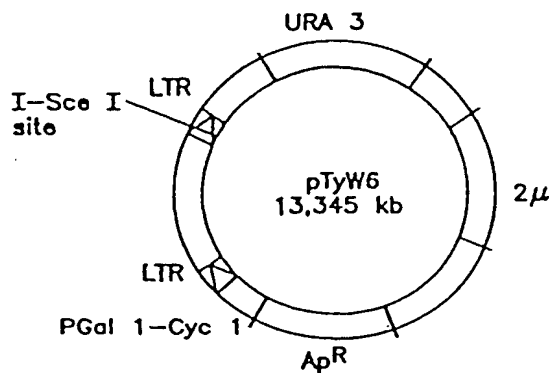
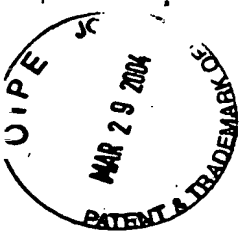


FIG. 10B



Construction: pGP 704 from De Lorenzo, with transposase gene and insertion of the linker[I-SceI] in NotI unique site

FIG. 11



Construction: pD 123, from J.D. Boeke
with insertion of a linker[I-SceI-NotI] in BamHI

FIG. 12

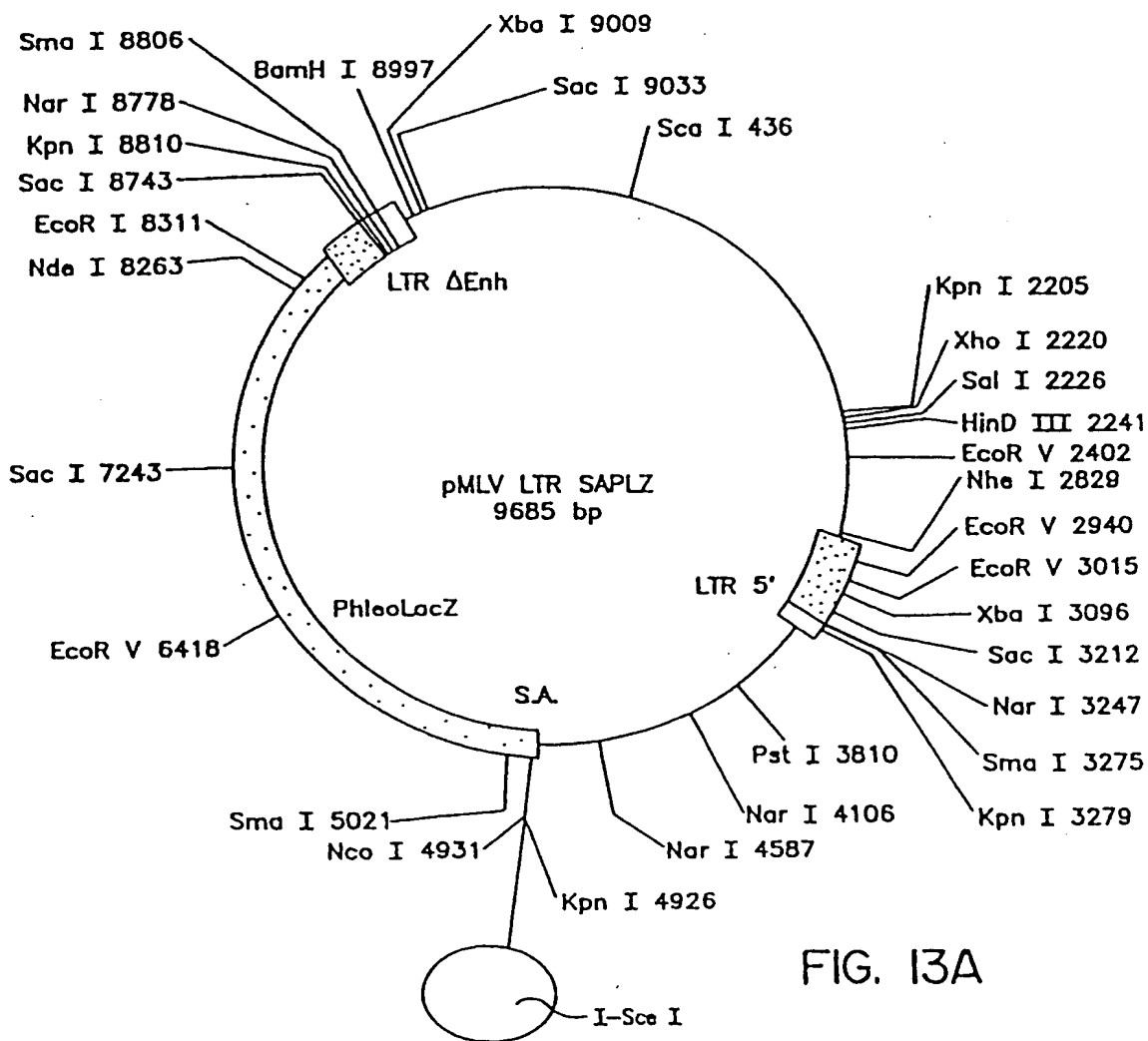


FIG. 13A

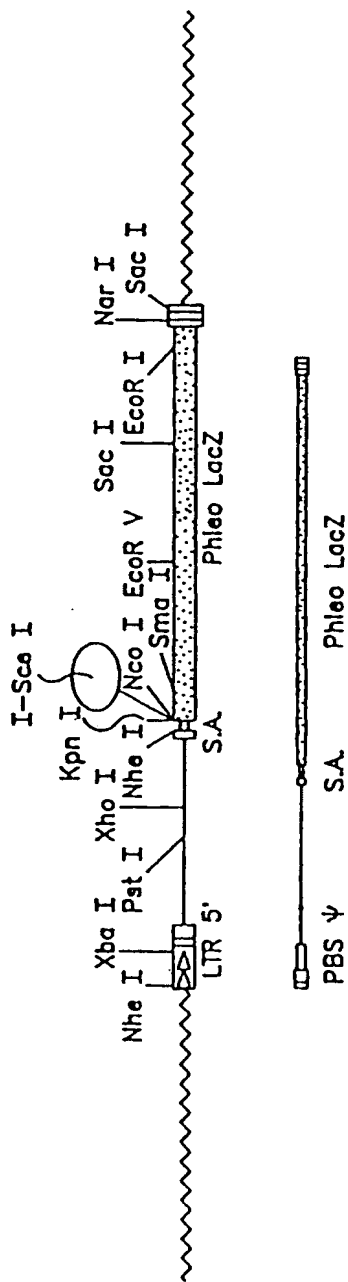


FIG. 13B

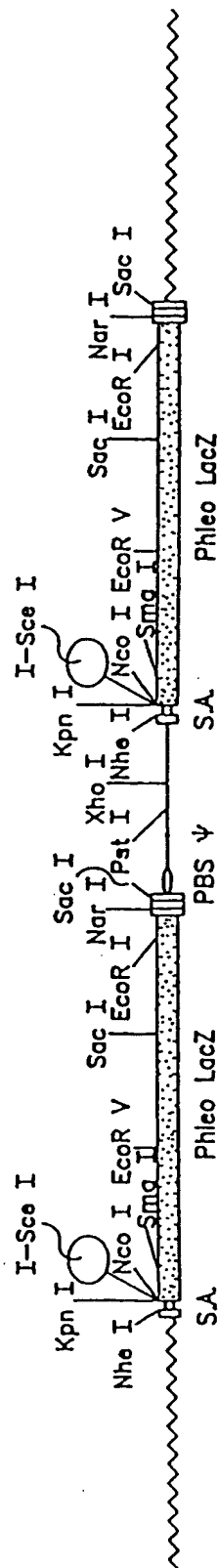
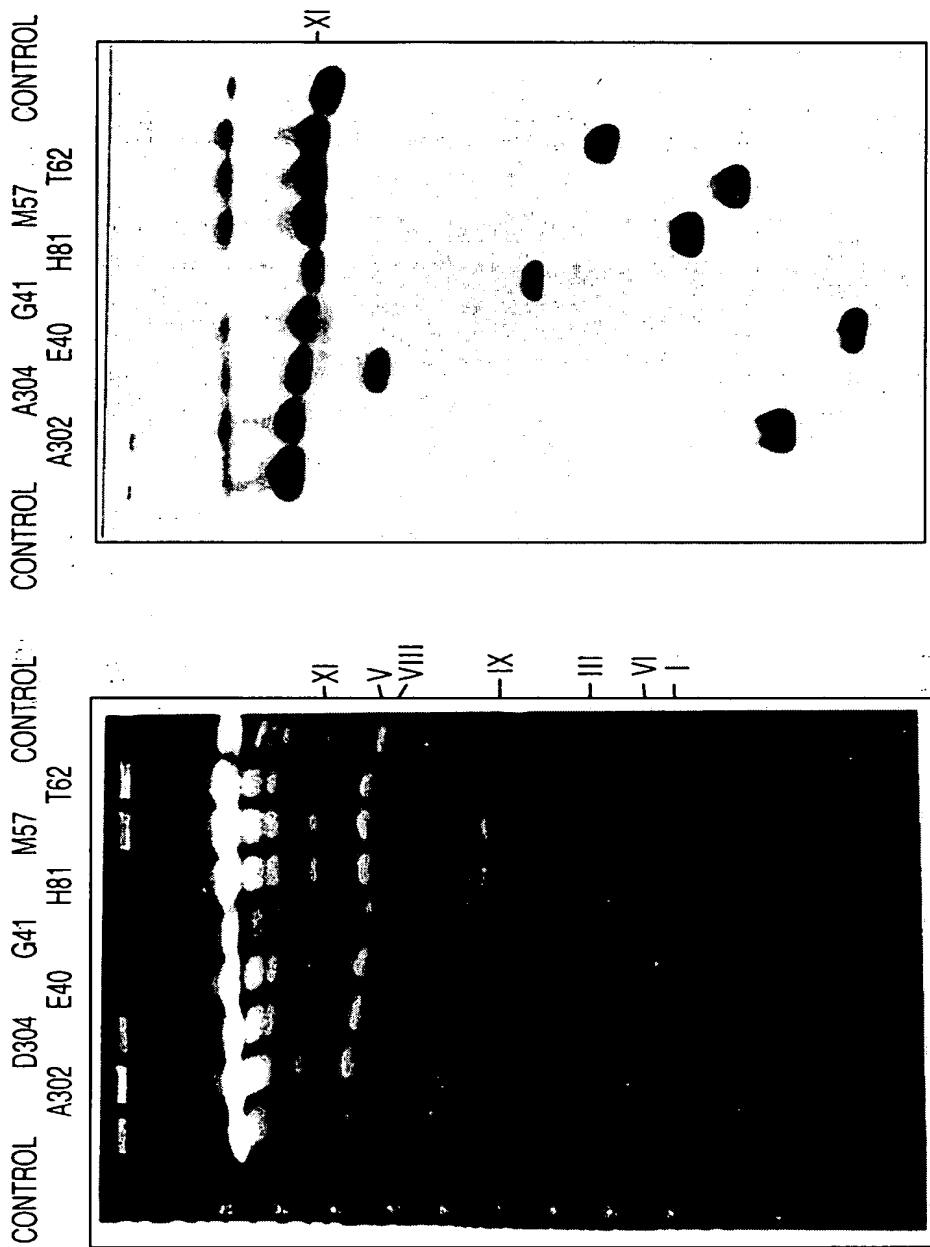


FIG. 13C

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LEFT END PROBE
COSMID pUKG 040

FIG. 14A

FIG. 14B

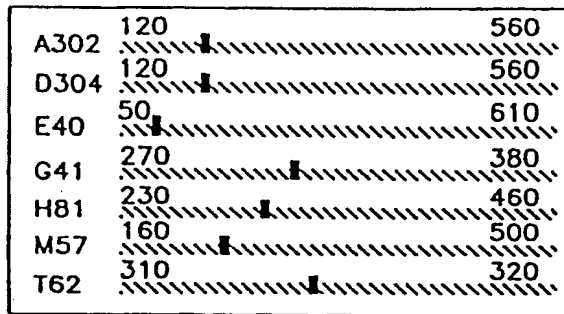
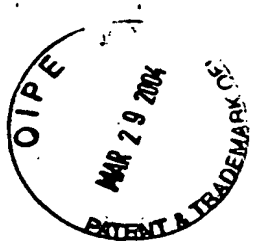


FIG. 15A

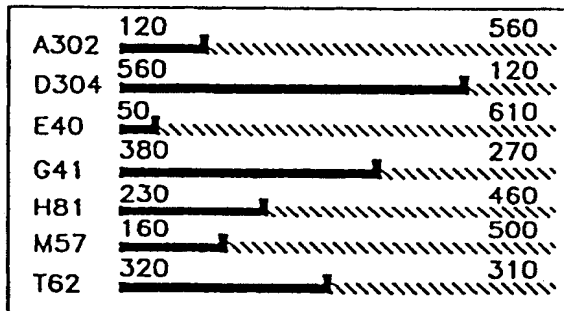


FIG. 15B

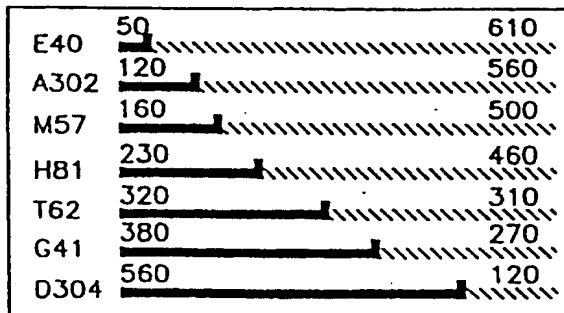


FIG. 15C

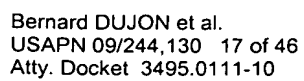


FIG. 15E

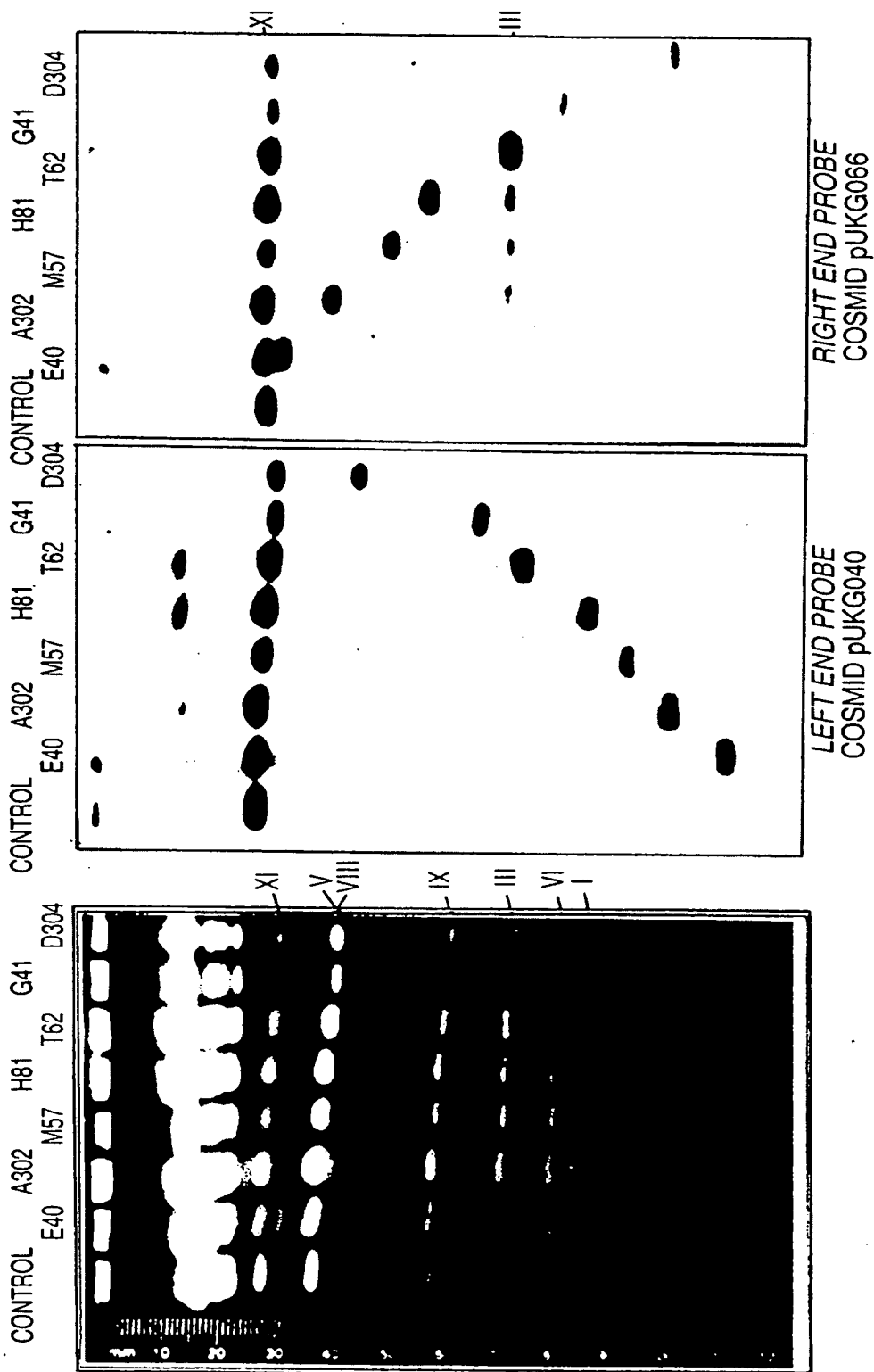
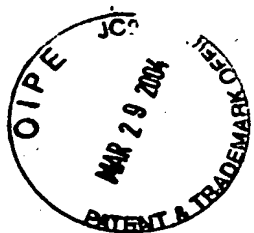


FIG. 16A

FIG. 16B

FIG. 16C

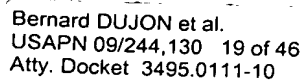
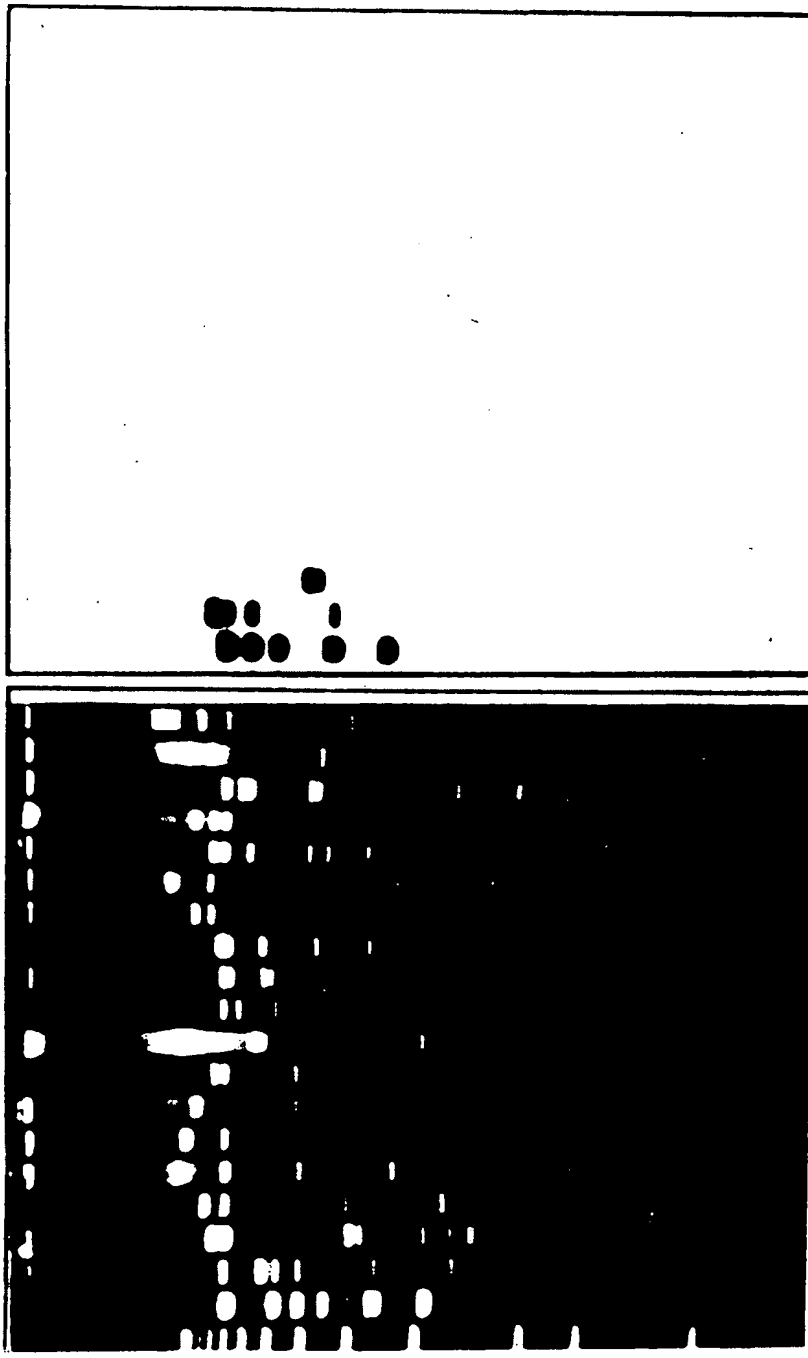
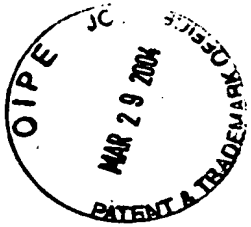
[illegible]

FIG. 17A

FIG. 17B



pEKG pEKG pEKG pEKG pEKG pEKG pUKG pUKG pUKG pUKG
019 097 081 121 119 021 146 144 046
pEKG pEKG pEKG pUKG pUKG pEKG pEKG pEKG pEKG pUKG
100 098 090 151 148 011 047 013 118 066

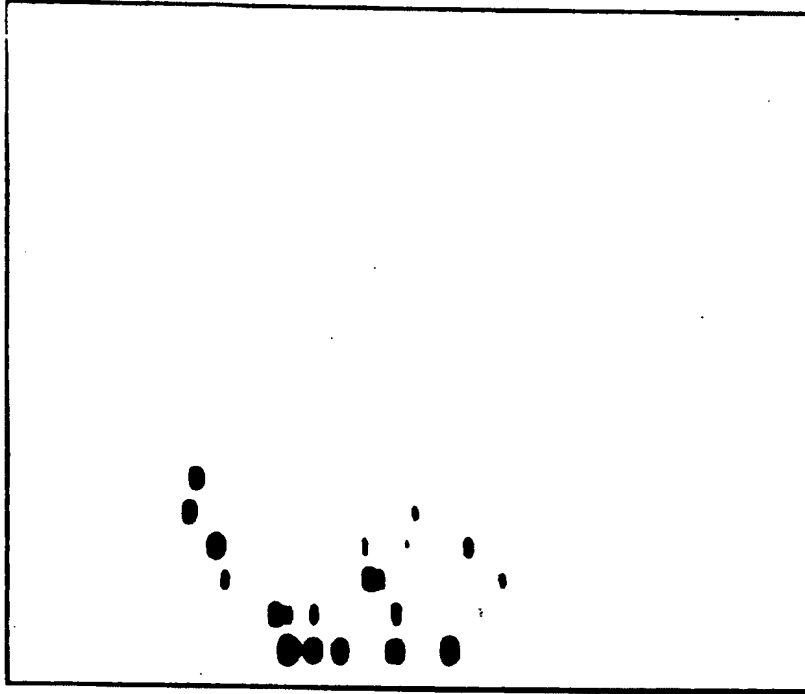


FIG. 17C

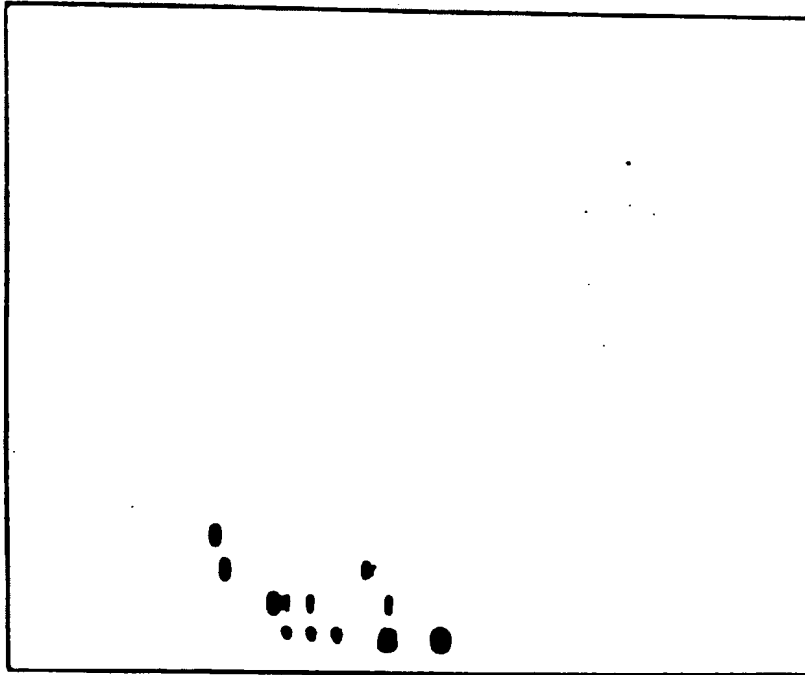
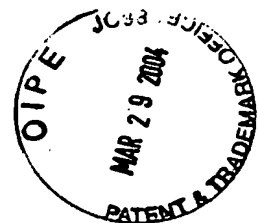


FIG. 17D



pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG
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pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG pKKG
100 098 090 151 148 011 047 013 118 066

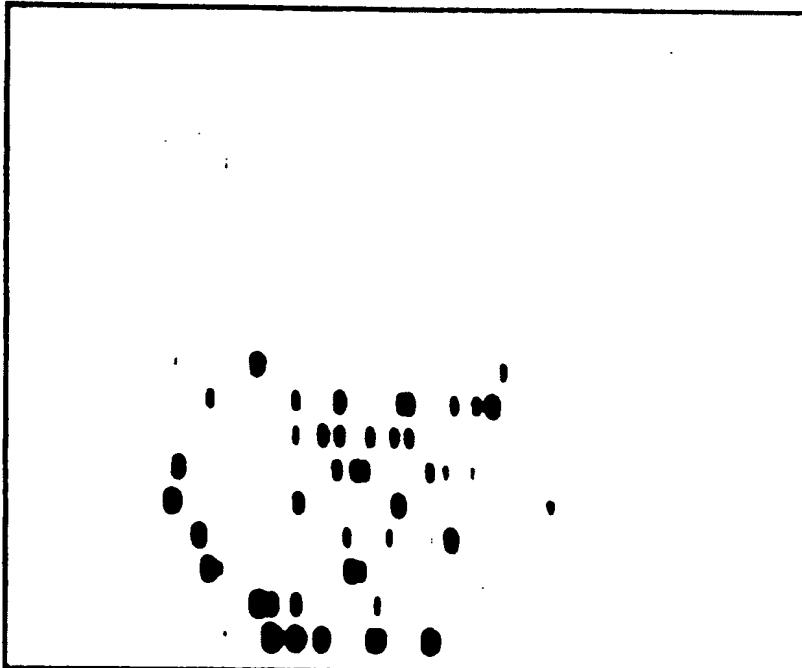


FIG. 17E

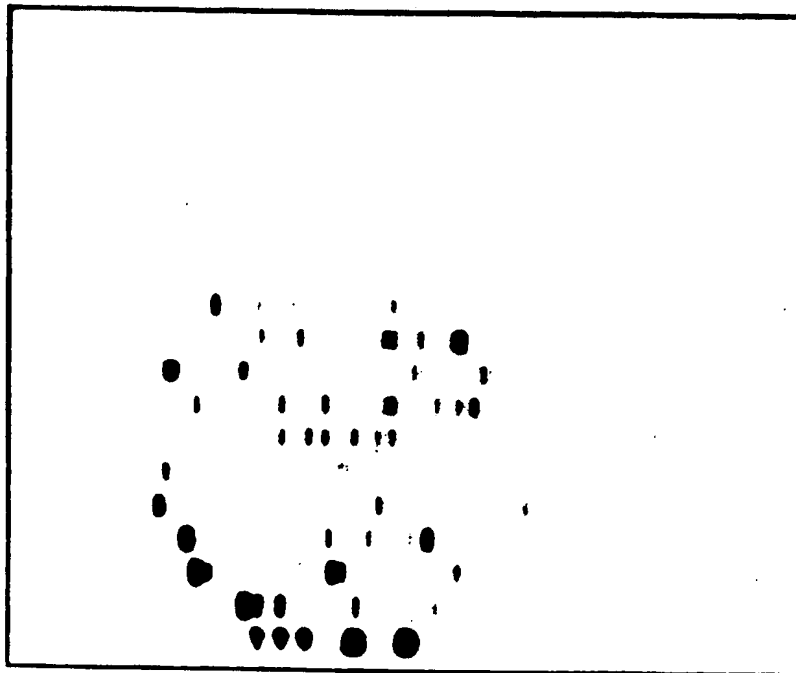


FIG. 17F

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PEKG PEKG PEKG PEKG PEKG PEKG PEKG PEKG PEKG PEKG
019 097 081 121 119 021 146 144 046
PEKG PEKG PEKG PEKG PEKG PEKG PEKG PEKG PEKG PEKG
100 098 090 151 148 011 047 013 118 066

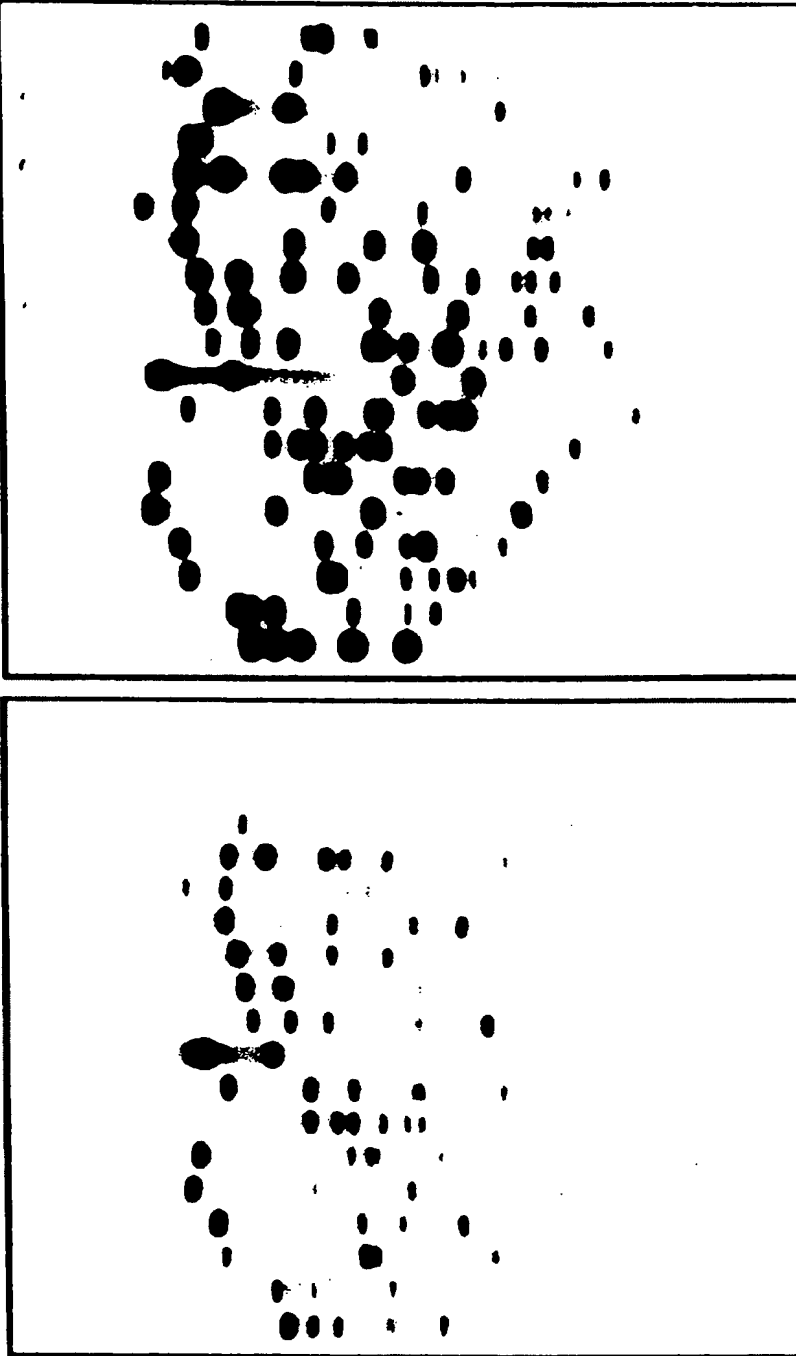


FIG. 17G

FIG. 17H

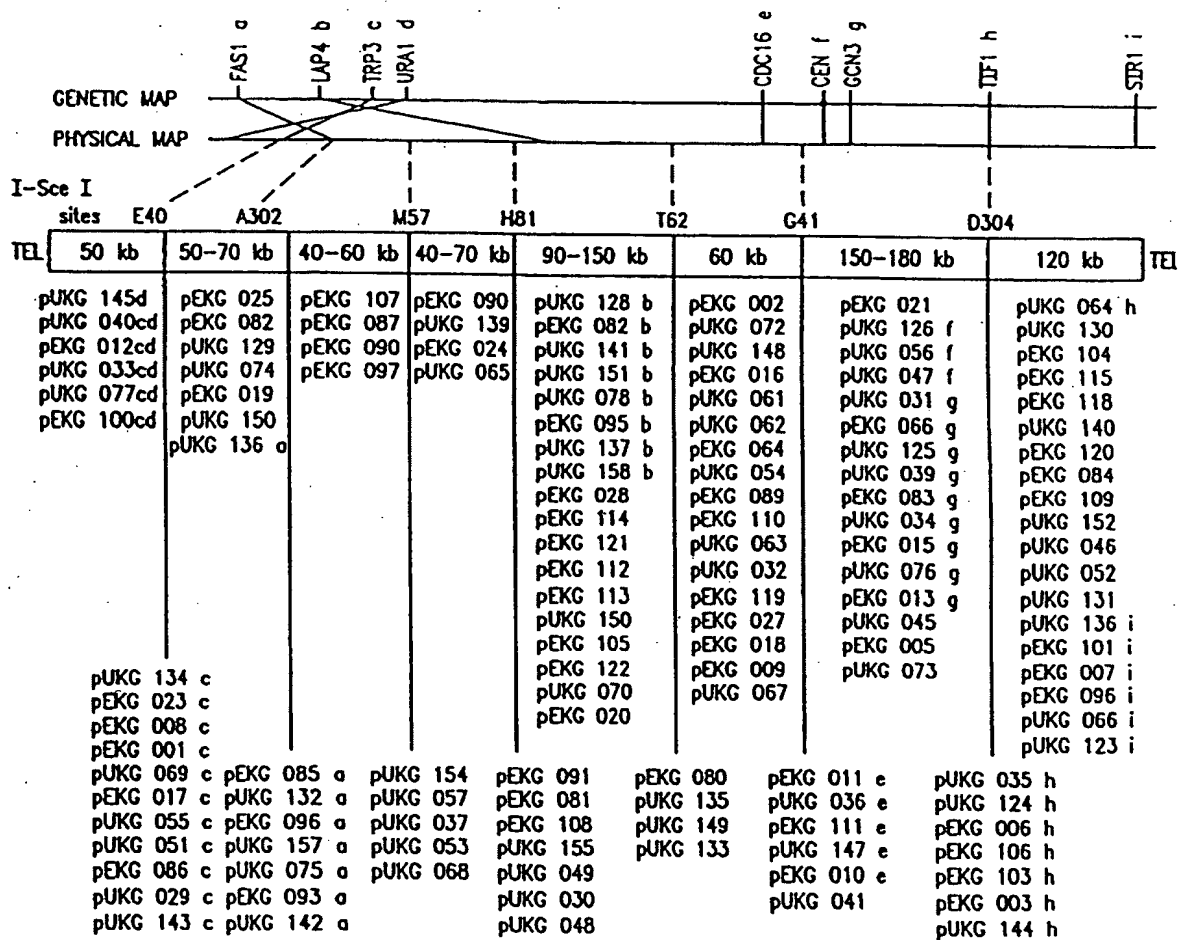
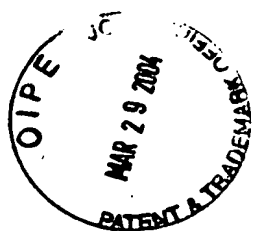


FIG. 18

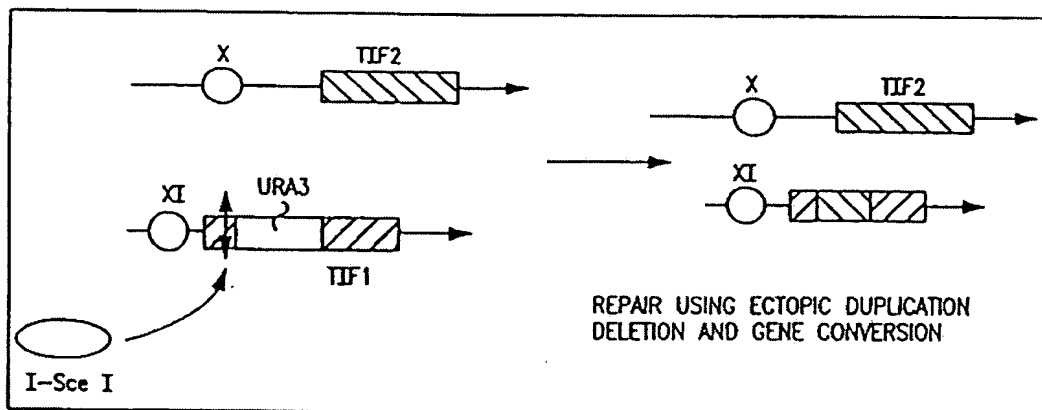
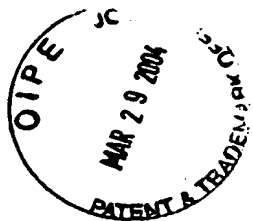


FIG. 19A

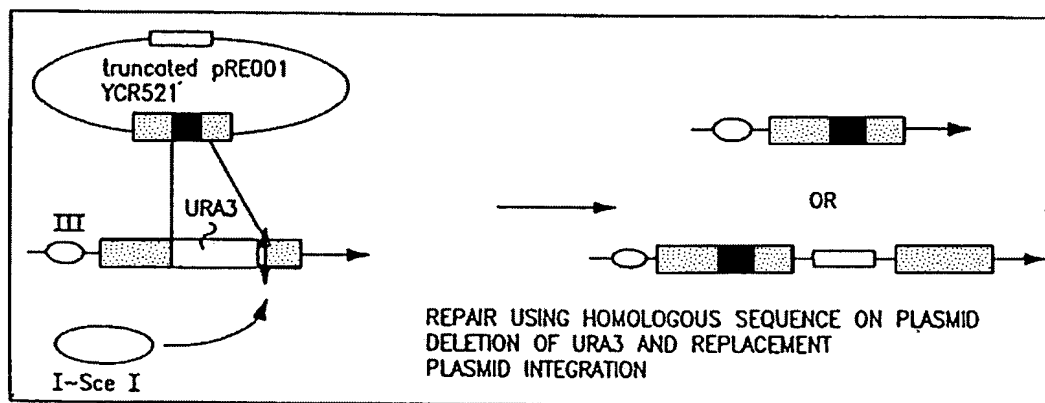


FIG. 19B

FIG. 20A

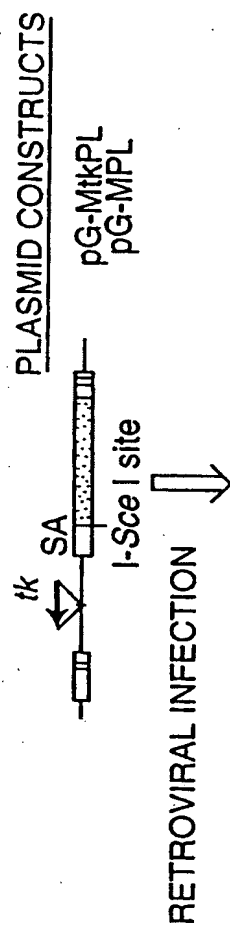


FIG. 20B

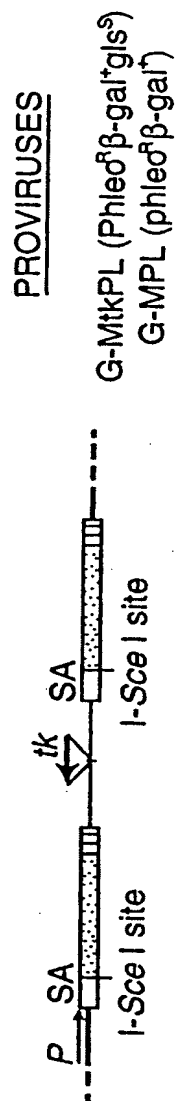


FIG. 20C

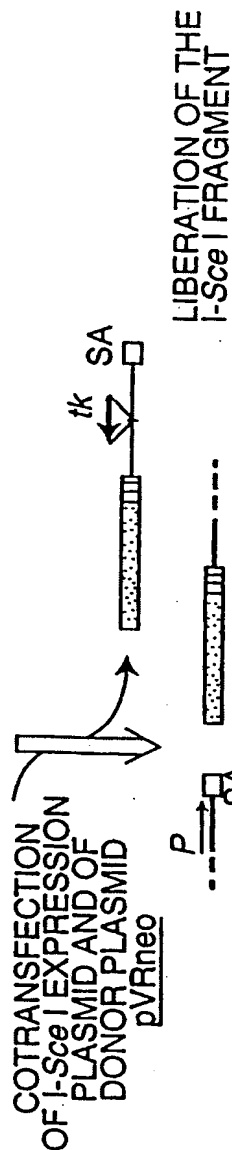


FIG. 20D

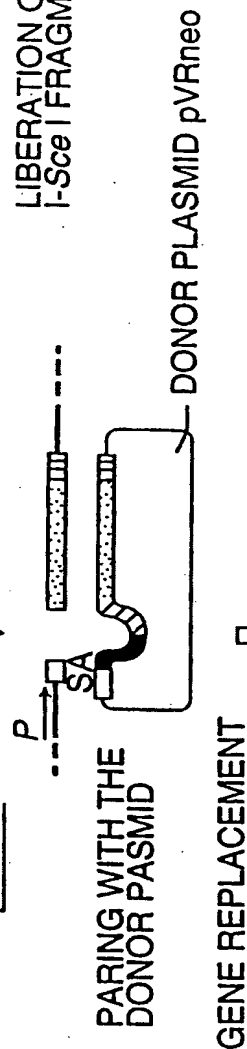
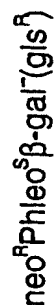


FIG. 20E



 LTR
 PhleoLacZ
 NEO
 POLY A
 — GENOMIC DNA
 ← *tk* THYMIDINE KINASE

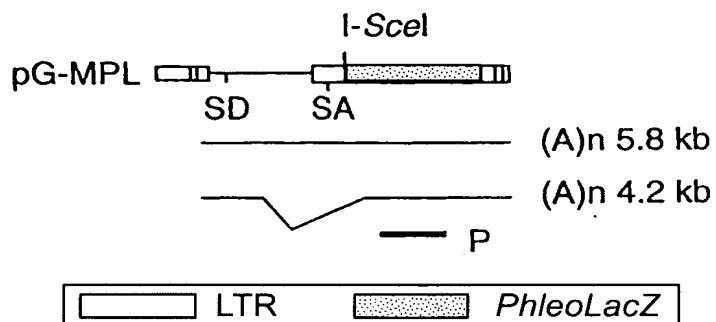
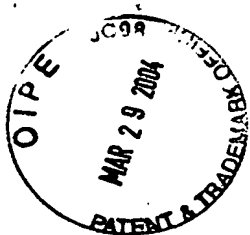


FIG. 2IA

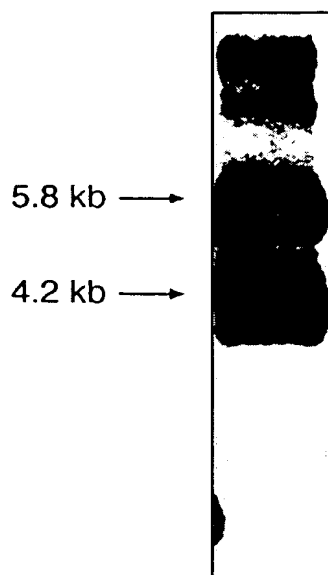
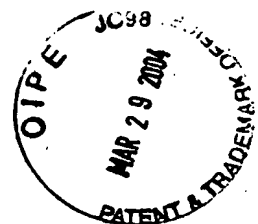
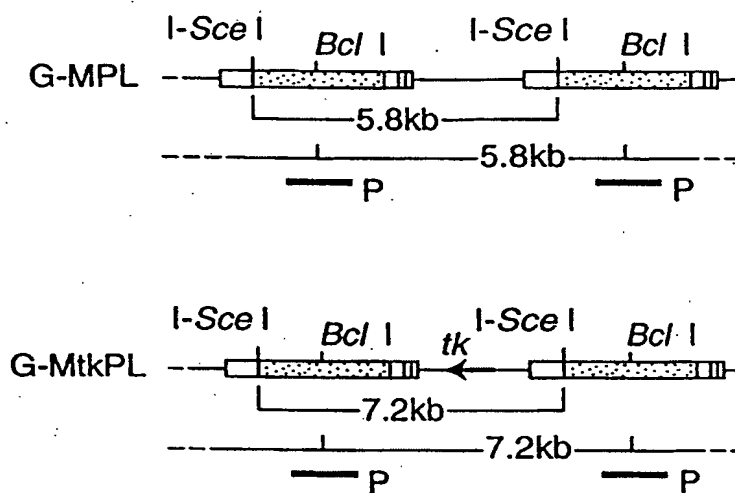
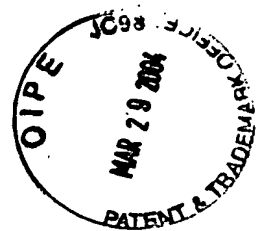


FIG. 21B



□ LTR
 ▨ *PhleoLacZ*
← *tk* THYMIDINE KINASE

FIG. 22A

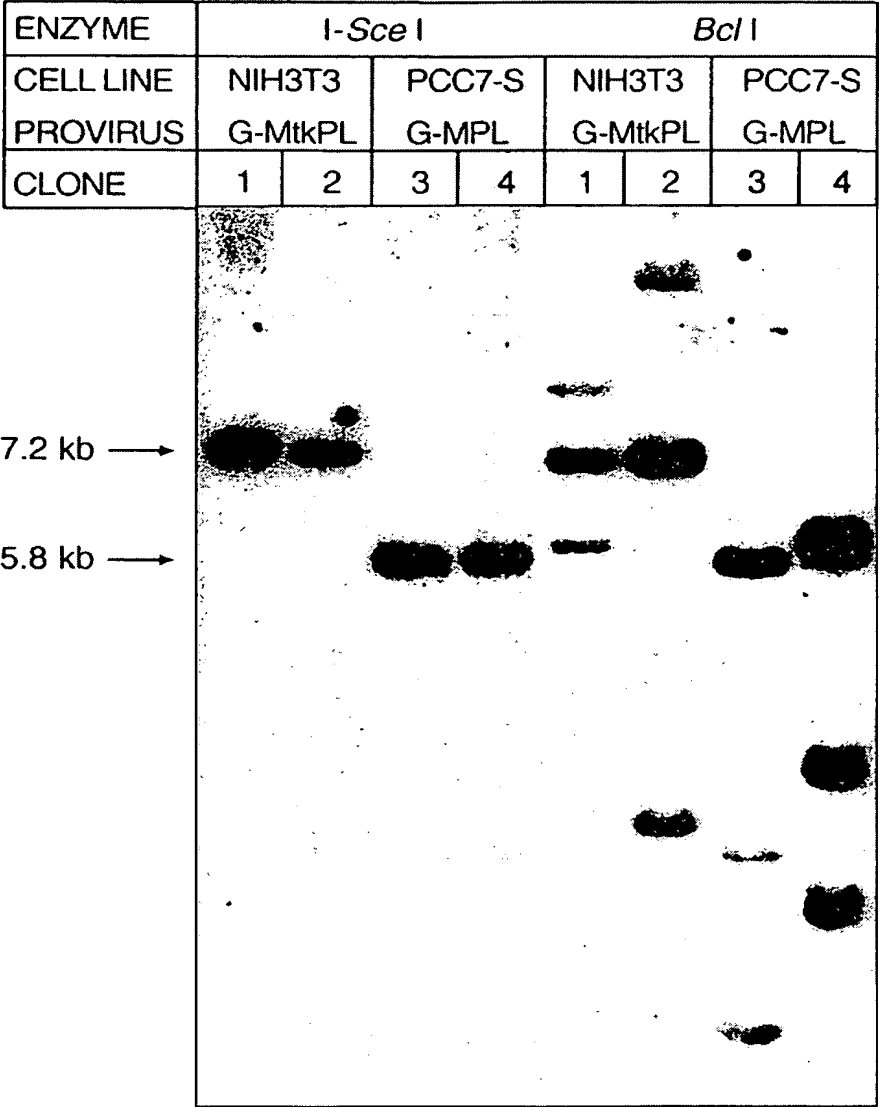
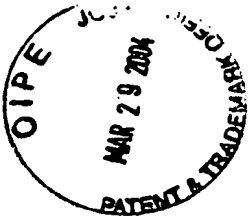
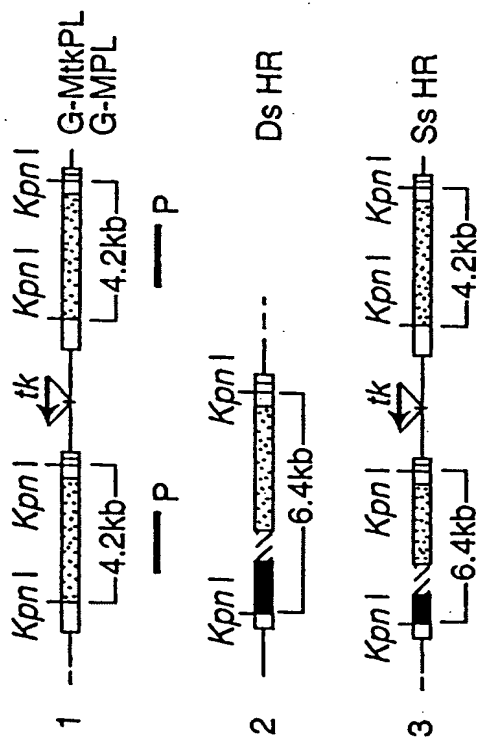
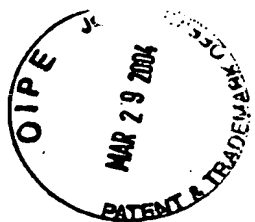


FIG. 22B



LTR
 Neo
 POLY A
 GENOMIC DNA
 tk
 THYMIDINE KINASE

FIG. 23A

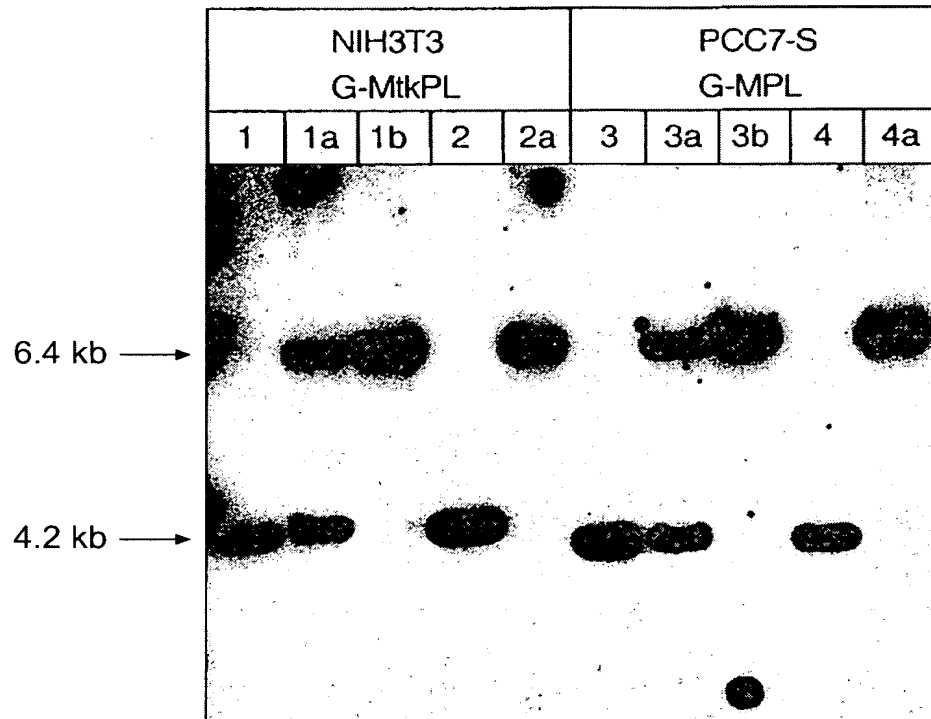
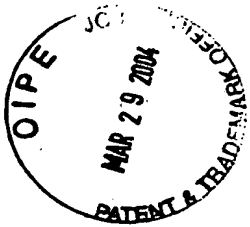
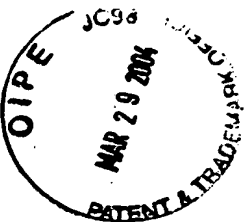


FIG. 23B



PCC7-S / G-MPL, CLONE 3

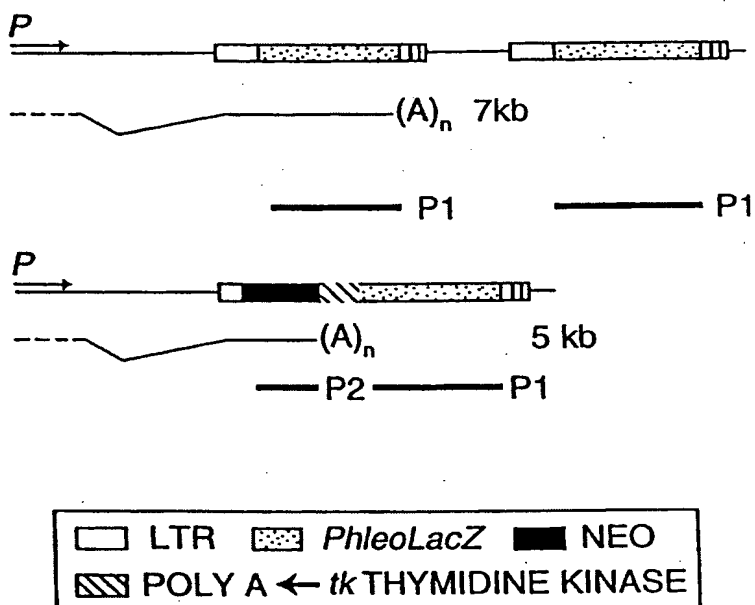


FIG. 24A

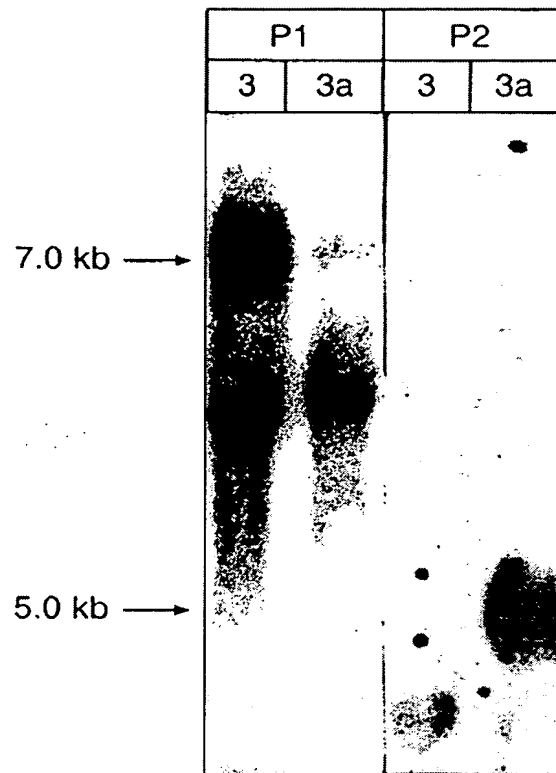
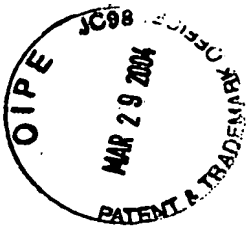


FIG. 24B

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A. CHROMOSOMAL DNA
CONTAINING PROVIRUS

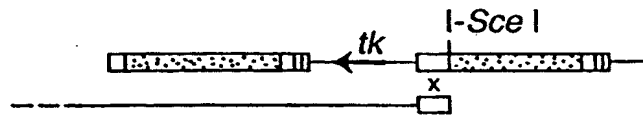
PHENOTYPES



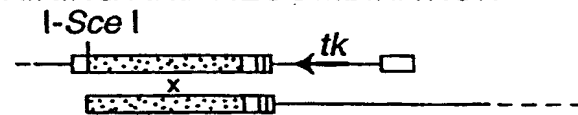
TRANSFECTION BY
I-Sce I ENDONUCLEASE
EXPRESSION VECTOR

B. INTRA-CHROMOSOMAL
RECOMBINATIONS EVENTS

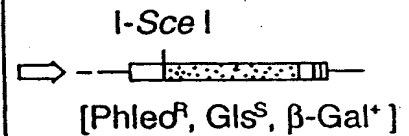
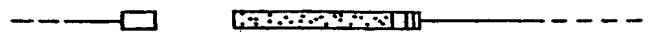
1. THE LEFT I-Sce I IS CUT.
PAIRING AND RECOMBINATION



2. THE RIGHT I-Sce I IS CUT.
PAIRING AND RECOMBINATION



3. BOTH I-Sce I SITES ARE CUT.
RELIGATION BY END-JOINING



C. INTER-CHROMOSOMAL RECOMBINATION EVENT
BOTH I-Sce I SITES ARE CUT. GAP REPAIR USING INTACT
CHROMOSOME SEQUENCES

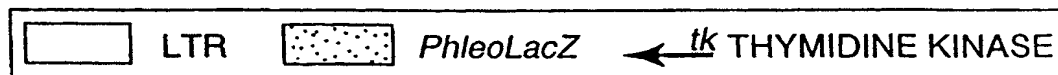
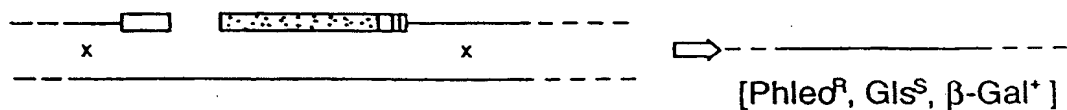
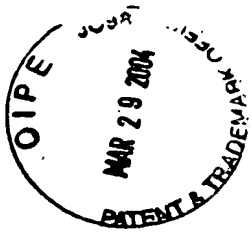


FIG. 25



A. PARENTAL DNA, G-MtkPL

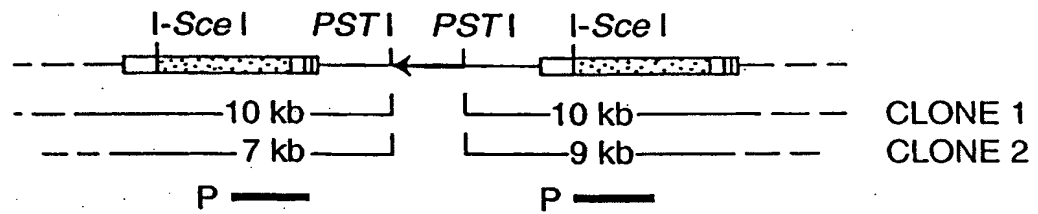


FIG. 26A

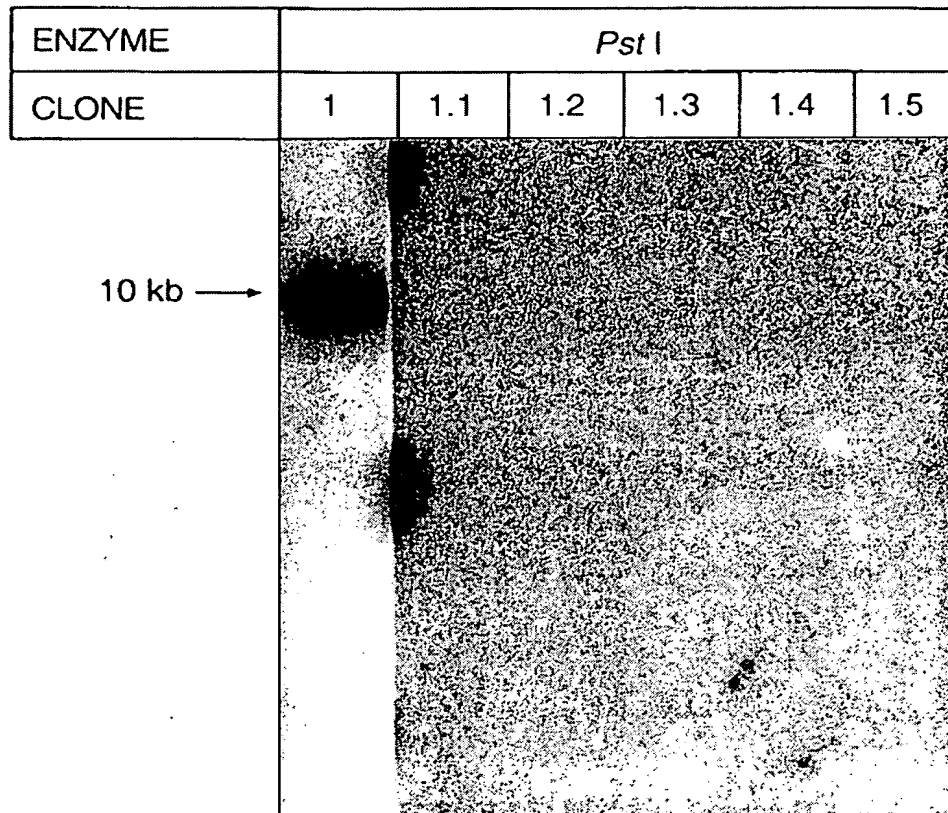
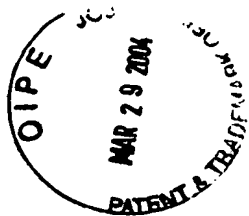


FIG. 26B

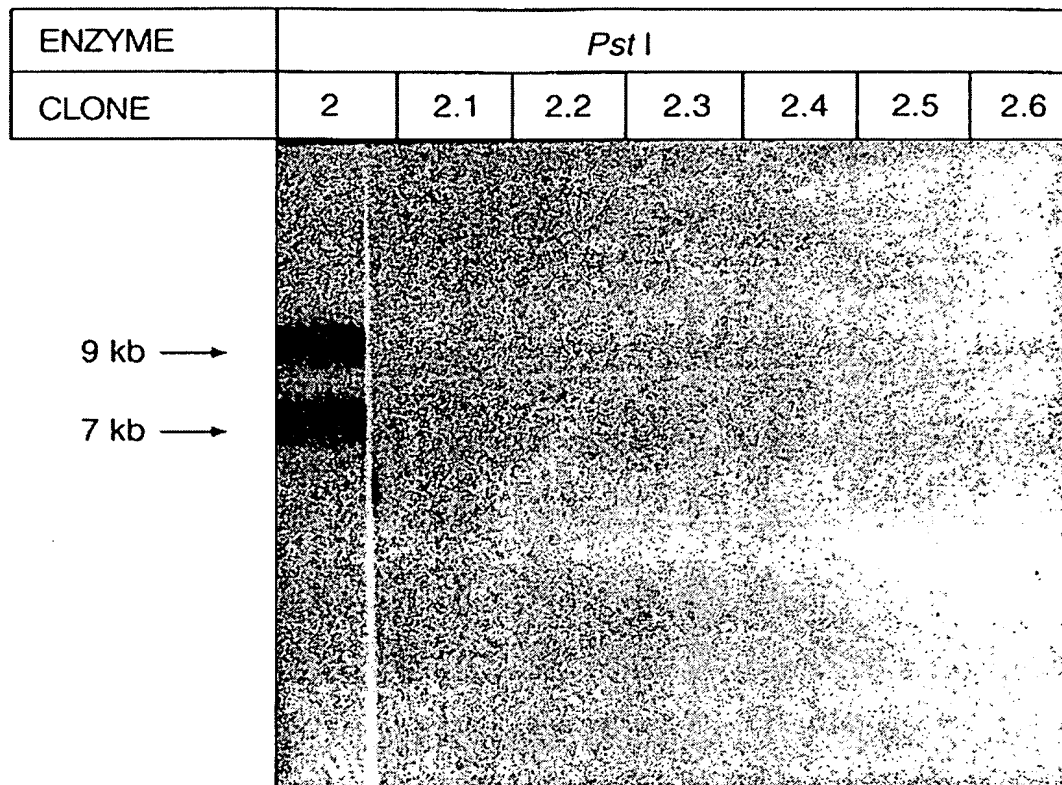
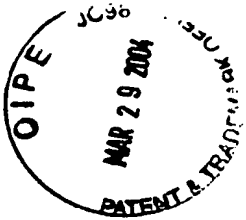
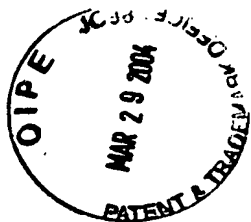
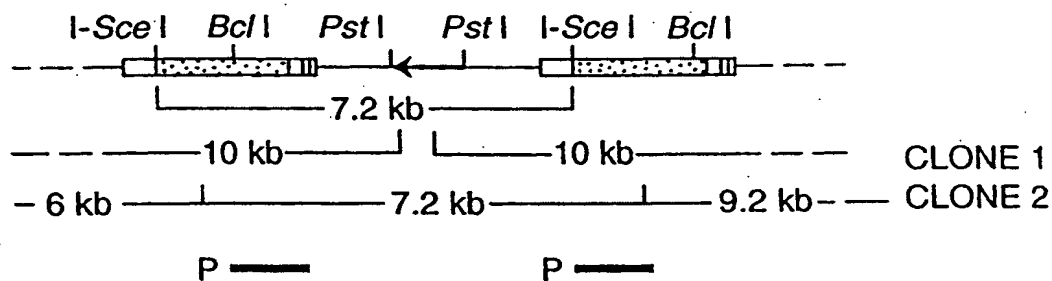


FIG. 26C



1. PARENTAL DNA, G-MtkPL



2. INTRA-MOLECULAR RECOMBINATION EVENT

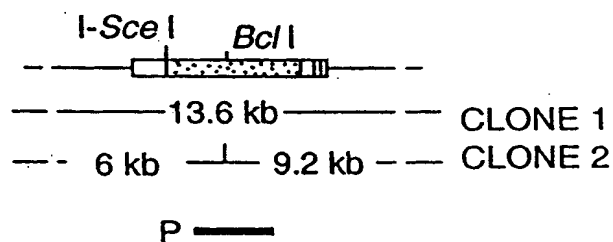


FIG. 27A

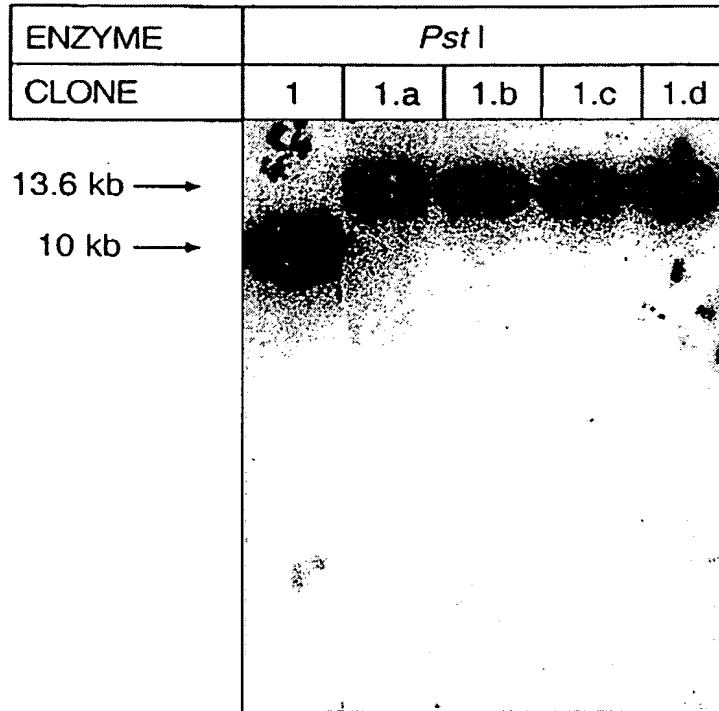
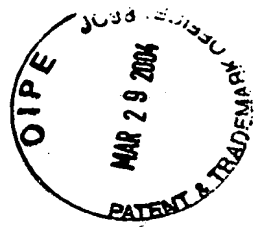


FIG. 27B

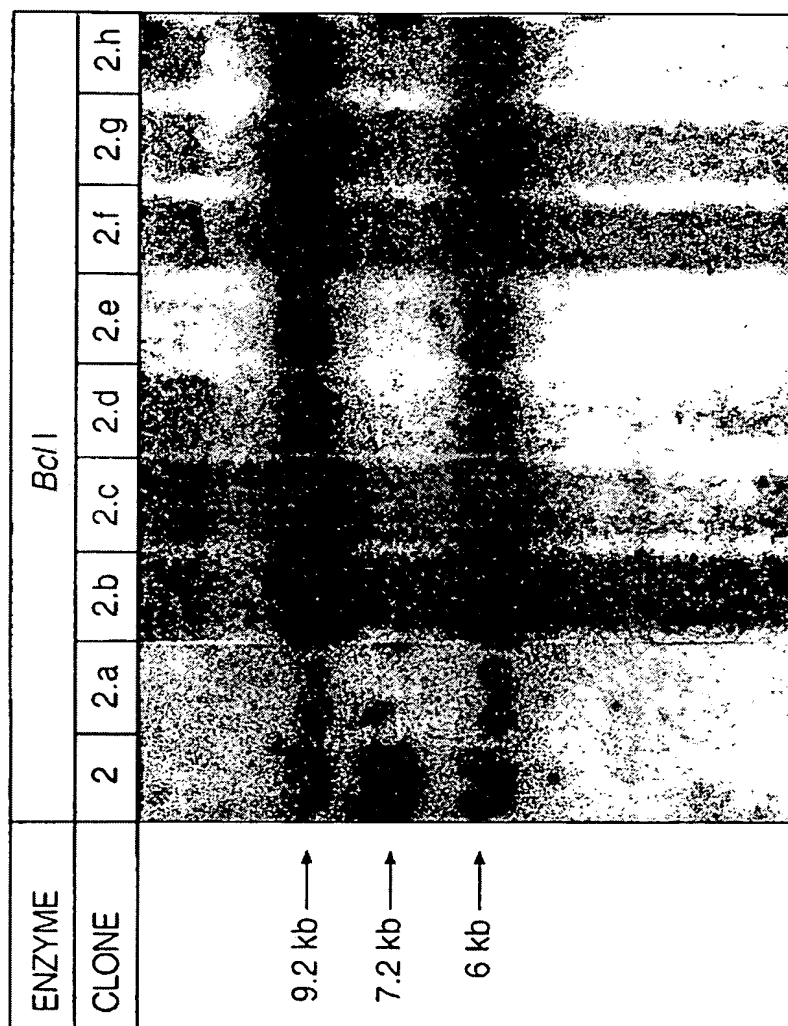
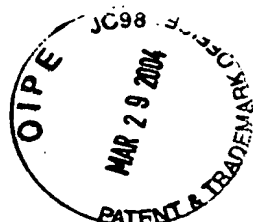
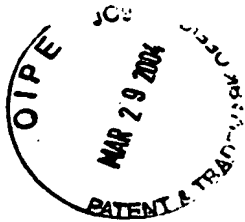
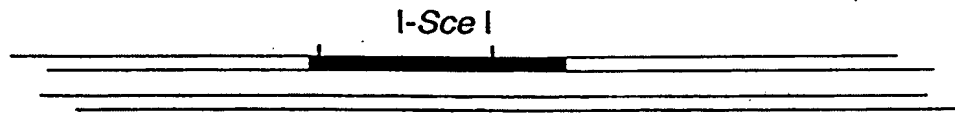


FIG. 27C

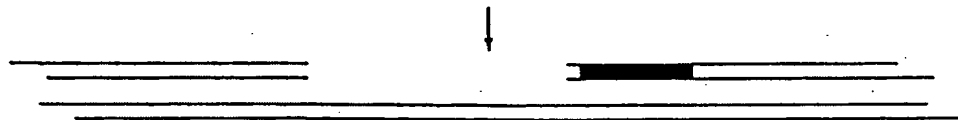


LOSS OF HETEROZYGOSITY

INTEGRATION OF ARTIFICIAL SITE OR
PRESENCE OF SPECIFIC SITE



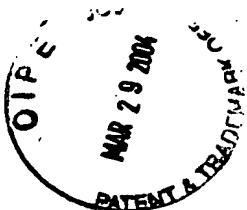
EXPRESSION OF I-Sce I AND SPECIFIC CLEAVAGE



REPAIR OF THE DSB WITH THE OTHER CHROMATID



FIG. 28



CONDITIONAL ACTIVATION (TANDEM REPEAT)

INTEGRATION OF ARTIFICIAL SITE BETWEEN
TANDEM REPEATS



GENE X INACTIVE

EXPRESSION OF I-Sce I AND SPECIFIC CLEAVAGE

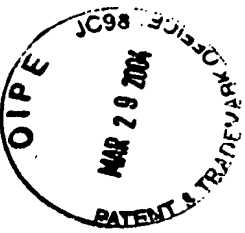


REPAIR OF THE DSB BY SINGLE STRAND ANNEALING



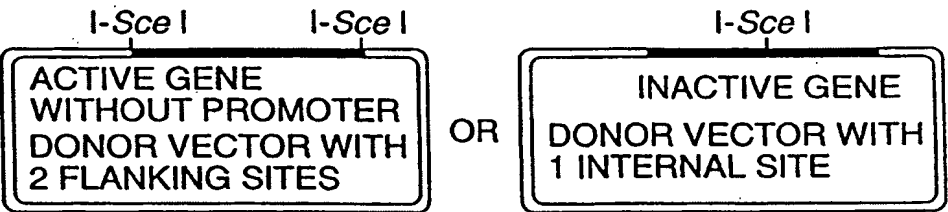
GENE X ACTIVE

FIG. 29

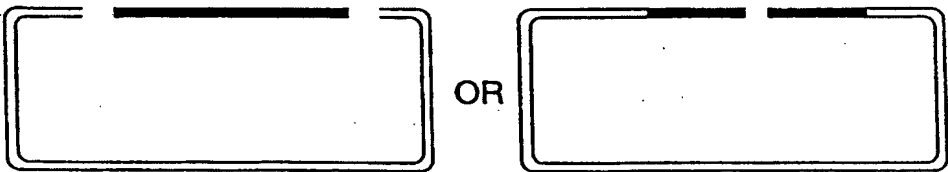


ONE STEP REARRANGEMENT

INTEGRATION OF ARTIFICIAL SITE OR
PRESENCE OF SPECIFIC SITE



EXPRESSION OF I-Sce I ENZYME
AND
SPECIFIC CLEAVAGE OF THE DONOR PLASMID



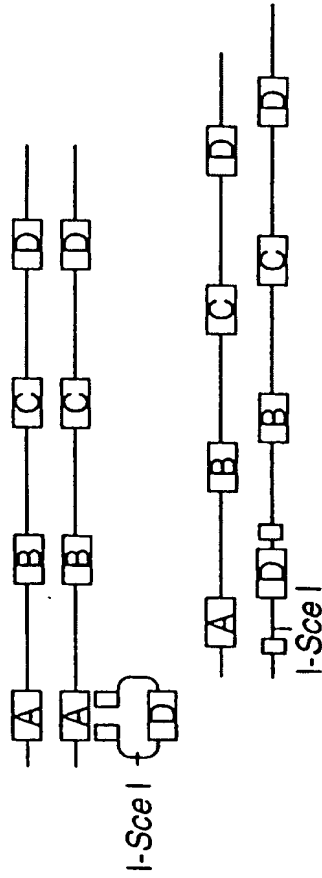
RECOMBINATION BETWEEN THE CHROMOSOME AND PLASMID



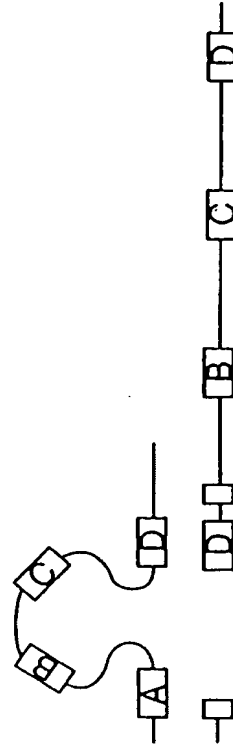
FIG. 30

DUPLICATION OF A LOCUS

1. INSERTION OF I-Sce I SITE BY CLASSICAL GENE REPLACEMENT



2. SPECIFIC CLEAVAGE BY I-Sce I ENZYME AND REPAIR OF THE BREAK BY HOMOLOGOUS SEQUENCES



3. DUPLICATION OF THE TOTALITY OF THE LOCUS

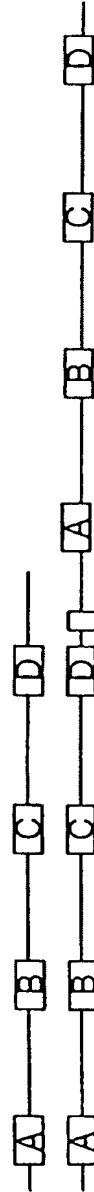
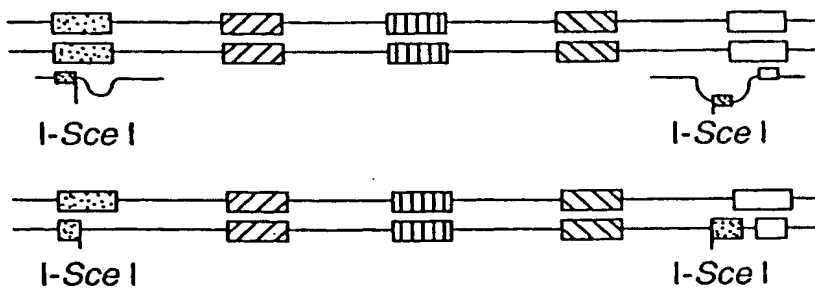


FIG. 31

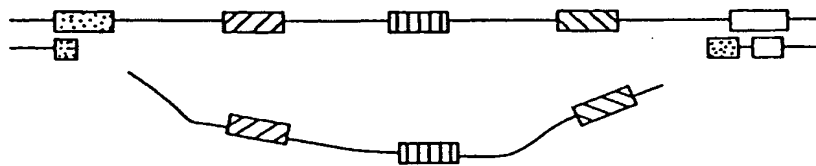


DELETION OF A LOCUS

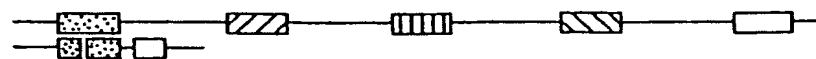
1 INSERTION OF TWO I-Sce I SITES FLANKING THE LOCUS



2 EXPRESSION OF THE ENZYME AND CLEAVAGE



3 RECOMBINATION BETWEEN THE TWO ENDS



4 DELETION OF THE LOCUS

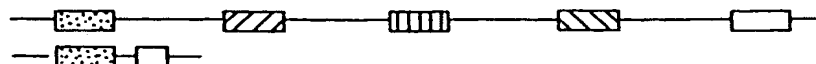


FIG. 32

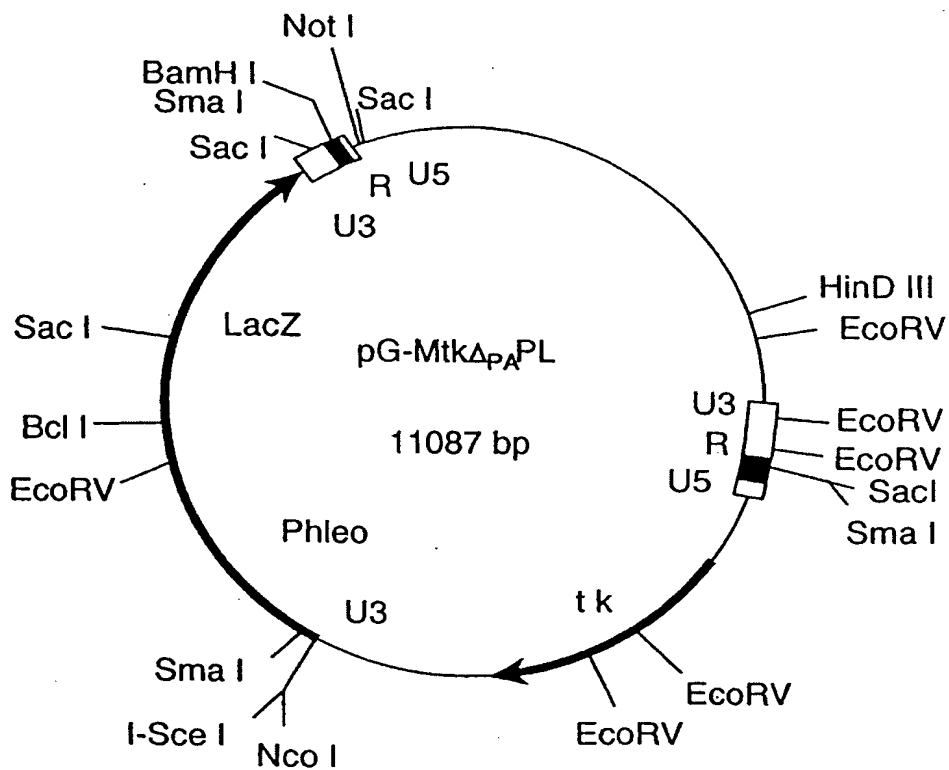


FIG. 33